

Study Title
COMBINED CHRONIC TOXICITY/ONCOGENICITY
STUDY 2-YEAR ORAL GAVAGE STUDY IN RATS

Laboratory Project ID:

Volume 6 of 13

NUMBER OF PAGES IN VOLUME: 338

- TEST GUIDELINES:**
- U.S. EPA Health Effects Test Guidelines OPPTS 870.4300 Combined Chronic Toxicity/Carcinogenicity (1998)
 - OECD Guidelines for the Testing of Chemicals Section 4 (No. 453) Health Effects (2009)
 - JMAFF Japan Agricultural Chemicals Regulation Law 12 Nousan No. 8147 (2000)
 - EEC Methods for the Determination of Toxicity Method B.33 Combined Chronic/Carcinogenicity test, Directive 88/302/EC (1988)

AUTHOR:

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PERFORMING LABORATORY:

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Table 8
Statistical Analysis of Non-Neoplastic Lesions

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
adrenal glands				
angiectasis/cystic degeneration, focal cortical				
Overall Rates (a)	17/70 (24.29%)	3/52 (5.77%)	1/52 (1.92%)	14/70 (20.00%)
Fisher's Exact Test; P-value		0.0065	0.0005	0.6844
Cochran-Armitage Trend Test; P-value		NT	NT	0.3965
atrophy, cortical				
Overall Rates (a)	1/70 (1.43%)	1/52 (1.92%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8063
hematopoiesis, extramedullary				
Overall Rates (a)	0/70 (0.00%)	0/52 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4262	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6723
hyperplasia, focal cortical				
Overall Rates (a)	16/70 (22.86%)	4/52 (7.69%)	10/52 (19.23%)	8/70 (11.43%)
Fisher's Exact Test; P-value		0.0279	0.6620	0.1152
Cochran-Armitage Trend Test; P-value		NT	NT	0.1798

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
adrenal glands				
hyperplasia, focal medullary				
Overall Rates (a)	10/70 (14.29%)	10/52 (19.23%)	11/52 (21.15%)	9/70 (12.86%)
Fisher's Exact Test; P-value		0.4714	0.3419	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8839
hypertrophy, focal cortical				
Overall Rates (a)	2/70 (2.86%)	2/52 (3.85%)	1/52 (1.92%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4852
infarct				
Overall Rates (a)	2/70 (2.86%)	0/52 (0.00%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.5068	0.5068	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.0722
necrosis				
Overall Rates (a)	1/70 (1.43%)	0/52 (0.00%)	0/52 (0.00%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4620

(a) - Number of animals with lesion/number of animals with the tissue examined

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Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
adrenal glands				
vacuolation, diffuse				
Overall Rates (a)	0/70 (0.00%)	0/52 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4262	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6723
vacuolation, focal				
Overall Rates (a)	23/70 (32.86%)	11/52 (21.15%)	10/52 (19.23%)	11/70 (15.71%)
Fisher's Exact Test; P-value		0.2203	0.1039	0.0293
Cochran-Armitage Trend Test; P-value		NT	0.0770	0.0167*
aorta				
mineralization				
Overall Rates (a)	5/70 (7.14%)	1/50 (2.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.3988	0.2382	0.0581
Cochran-Armitage Trend Test; P-value		NT	0.1325	0.0151*
bone marrow, femur				
hyperplasia, granulocytic				
Overall Rates (a)	2/70 (2.86%)	1/50 (2.00%)	1/52 (1.92%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9931

(a) - Number of animals with lesion/number of animals with the tissue examined

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Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
bone marrow, femur				
hyperplasia, mixed				
Overall Rates (a)	0/70 (0.00%)	1/50 (2.00%)	1/52 (1.92%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.4167	0.4262	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4672
necrosis				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2048
bone marrow, sternum				
hyperplasia, granulocytic				
Overall Rates (a)	1/70 (1.43%)	1/50 (2.00%)	1/52 (1.92%)	3/70 (4.29%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.6195
Cochran-Armitage Trend Test; P-value		NT	NT	0.3008
hyperplasia, mixed				
Overall Rates (a)	0/70 (0.00%)	1/50 (2.00%)	1/52 (1.92%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.4167	0.4262	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4672

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
bone, femur				
fibrous osteodystrophy				
Overall Rates (a)	4/70 (5.71%)	0/51 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.1373	0.3924	0.1196
Cochran-Armitage Trend Test; P-value		NT	0.1781	0.0359*
hyperostosis				
Overall Rates (a)	1/70 (1.43%)	0/51 (0.00%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2046
osteoarthritis/pododermatitis				
Overall Rates (a)	0/70 (0.00%)	1/51 (1.96%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4215	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6716
bone, sternum				
fibrous osteodystrophy				
Overall Rates (a)	3/70 (4.29%)	0/50 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.2647	0.6354	0.2446
Cochran-Armitage Trend Test; P-value		NT	NT	0.0884

(a) - Number of animals with lesion/number of animals with the tissue examined

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Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
bone, sternum				
hyperostosis				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2048
brain				
compression, ventral (pituitary tumor)				
Overall Rates (a)	22/70 (31.43%)	15/50 (30.00%)	16/52 (30.77%)	17/70 (24.29%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4510
Cochran-Armitage Trend Test; P-value		NT	NT	0.3846
edema				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2073
hemorrhage				
Overall Rates (a)	1/70 (1.43%)	1/50 (2.00%)	0/52 (0.00%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6766

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NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
brain				
inflammation, embolic				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2073
mineralization, focal				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2073
necrosis, focal				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2073
schwannoma, malignant, secondary				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2073

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
cavity, abdominal				
fibrosarcoma, malignant, secondary				
Overall Rates (a)	0/1 (0.00%)	0/1 (0.00%)	0/2 (0.00%)	1/3 (33.33%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.3496
inflammation, acute				
Overall Rates (a)	0/1 (0.00%)	1/1 (100.00%)	0/2 (0.00%)	0/3 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.3496
coagulating glands				
depletion, secretory				
Overall Rates (a)	4/70 (5.71%)	3/50 (6.00%)	5/53 (9.43%)	5/70 (7.14%)
Fisher's Exact Test; P-value		1.0000	0.4973	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6117
dilatation				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	1/53 (1.89%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4309	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6767

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NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
coagulating glands				
hyperplasia				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/53 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2071
inflammation				
Overall Rates (a)	5/70 (7.14%)	4/50 (8.00%)	3/53 (5.66%)	5/70 (7.14%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8980
epididymides				
granuloma, spermatic				
Overall Rates (a)	0/70 (0.00%)	1/50 (2.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4167	0.4262	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9961
inflammation, peritoneal				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9961

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
epididymides				
oligospermia/germ cell debris, bilateral				
Overall Rates (a)	6/70 (8.57%)	3/50 (6.00%)	4/52 (7.69%)	4/70 (5.71%)
Fisher's Exact Test; P-value		0.7334	1.0000	0.7447
Cochran-Armitage Trend Test; P-value		NT	NT	0.5865
oligospermia/germ cell debris, unilateral				
Overall Rates (a)	2/70 (2.86%)	4/50 (8.00%)	2/52 (3.85%)	4/70 (5.71%)
Fisher's Exact Test; P-value		0.2331	1.0000	0.6806
Cochran-Armitage Trend Test; P-value		NT	NT	0.6270
polyarteritis				
Overall Rates (a)	0/70 (0.00%)	1/50 (2.00%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4167	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6708
esophagus				
hemorrhage				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2073

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
esophagus				
inflammation				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2048
eyes				
cataract				
Overall Rates (a)	3/68 (4.41%)	3/49 (6.12%)	1/51 (1.96%)	3/70 (4.29%)
Fisher's Exact Test; P-value		0.6938	0.6342	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.7511
hemorrhage				
Overall Rates (a)	0/68 (0.00%)	1/49 (2.04%)	1/51 (1.96%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4188	0.4286	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9840
inflammation				
Overall Rates (a)	0/68 (0.00%)	0/49 (0.00%)	1/51 (1.96%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4286	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6840

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
eyes				
inflammation, acute				
Overall Rates (a)	1/68 (1.47%)	0/49 (0.00%)	2/51 (3.92%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	0.5757	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6926
metaplasia, squamous				
Overall Rates (a)	3/68 (4.41%)	1/49 (2.04%)	1/51 (1.96%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.6387	0.6342	0.1169
Cochran-Armitage Trend Test; P-value		NT	NT	0.0816
neovascularization, corneal				
Overall Rates (a)	3/68 (4.41%)	1/49 (2.04%)	0/51 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.6387	0.2591	0.1169
Cochran-Armitage Trend Test; P-value		NT	0.1171	0.0317*
synechia				
Overall Rates (a)	0/68 (0.00%)	0/49 (0.00%)	0/51 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2115

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
eyes, optic nerves				
necrosis				
Overall Rates (a)	0/70 (0.00%)	0/49 (0.00%)	0/51 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2088
eyes, retina				
degeneration/atrophy, retina, unilateral				
Overall Rates (a)	0/63 (0.00%)	0/42 (0.00%)	1/43 (2.33%)	1/63 (1.59%)
Fisher's Exact Test; P-value		1.0000	0.4057	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2393
detachment, retinal				
Overall Rates (a)	0/63 (0.00%)	0/42 (0.00%)	0/43 (0.00%)	1/63 (1.59%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2127
fold/rosette, retinal				
Overall Rates (a)	1/63 (1.59%)	1/42 (2.38%)	1/43 (2.33%)	0/63 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4669

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
foot/feet				
fracture/callus				
Overall Rates (a)	0/1 (0.00%)	0/3 (0.00%)	0/1 (0.00%)	1/2 (50.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1736
inflammation				
Overall Rates (a)	0/1 (0.00%)	2/3 (66.67%)	1/1 (100.00%)	0/2 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6304
osteoarthritis/pododermatitis				
Overall Rates (a)	1/1 (100.00%)	1/3 (33.33%)	0/1 (0.00%)	1/2 (50.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6304
harderian glands				
hyperplasia, focal				
Overall Rates (a)	13/68 (19.12%)	11/50 (22.00%)	8/52 (15.38%)	9/70 (12.86%)
Fisher's Exact Test; P-value		0.8177	0.6362	0.3584
Cochran-Armitage Trend Test; P-value		NT	NT	0.2365

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
heart				
bacterial colonies				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2073
cardiomyopathy				
Overall Rates (a)	63/70 (90.00%)	45/50 (90.00%)	46/52 (88.46%)	64/70 (91.43%)
Fisher's Exact Test; P-value		1.0000	0.7766	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8424
endocarditis, valvular vegetative				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	1/52 (1.92%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	0.4262	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2341
mineralization, myofiber				
Overall Rates (a)	2/70 (2.86%)	0/50 (0.00%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.5098	0.5068	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.0723

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
heart				
mineralization, vascular				
Overall Rates (a)	2/70 (2.86%)	0/50 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.5098	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.2195
thrombus				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9961
joint, tibiofemoral				
degeneration/necrosis, cartilage				
Overall Rates (a)	0/70 (0.00%)	0/51 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2059
inflammation, subacute/chronic				
Overall Rates (a)	0/70 (0.00%)	0/51 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4262	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6741

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
joint, tibiofemoral				
osteoarthritis/pododermatitis				
Overall Rates (a)	0/70 (0.00%)	1/51 (1.96%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4215	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6716
kidneys				
bacterial colonies				
Overall Rates (a)	0/70 (0.00%)	0/55 (0.00%)	0/53 (0.00%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.0695
carcinoma, sebaceous cell, malignant, secondary				
Overall Rates (a)	0/70 (0.00%)	0/55 (0.00%)	0/53 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2003
cyst				
Overall Rates (a)	5/70 (7.14%)	6/55 (10.91%)	1/53 (1.89%)	2/70 (2.86%)
Fisher's Exact Test; P-value		0.5335	0.2345	0.4411
Cochran-Armitage Trend Test; P-value		NT	NT	0.1045

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
kidneys				
dilatation, tubular				
Overall Rates (a)	4/70 (5.71%)	0/55 (0.00%)	3/53 (5.66%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.1298	1.0000	0.3659
Cochran-Armitage Trend Test; P-value		NT	NT	0.3647
hemorrhage				
Overall Rates (a)	0/70 (0.00%)	0/55 (0.00%)	0/53 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2003
hyaline, droplets, increased				
Overall Rates (a)	1/70 (1.43%)	0/55 (0.00%)	2/53 (3.77%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	0.5770	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.3332
hydronephrosis, bilateral				
Overall Rates (a)	13/70 (18.57%)	5/55 (9.09%)	8/53 (15.09%)	6/70 (8.57%)
Fisher's Exact Test; P-value		0.1991	0.6387	0.1372
Cochran-Armitage Trend Test; P-value		NT	NT	0.1533

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
kidneys				
hydronephrosis, unilateral				
Overall Rates (a)	7/70 (10.00%)	4/55 (7.27%)	2/53 (3.77%)	8/70 (11.43%)
Fisher's Exact Test; P-value		0.7540	0.2973	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9098
hyperplasia, transitional cell				
Overall Rates (a)	7/70 (10.00%)	5/55 (9.09%)	2/53 (3.77%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	0.2973	0.1654
Cochran-Armitage Trend Test; P-value		NT	0.2181	0.0497*
hyperplasia, tubular				
Overall Rates (a)	1/70 (1.43%)	0/55 (0.00%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2027
inflammation, chronic-active				
Overall Rates (a)	0/70 (0.00%)	0/55 (0.00%)	1/53 (1.89%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4309	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6678

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
kidneys				
inflammation, embolic				
Overall Rates (a)	0/70 (0.00%)	0/55 (0.00%)	0/53 (0.00%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.0695
mineralization, pelvic				
Overall Rates (a)	6/70 (8.57%)	2/55 (3.64%)	3/53 (5.66%)	6/70 (8.57%)
Fisher's Exact Test; P-value		0.4642	0.7307	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9034
mineralization, tubular				
Overall Rates (a)	6/70 (8.57%)	4/55 (7.27%)	4/53 (7.55%)	8/70 (11.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.7792
Cochran-Armitage Trend Test; P-value		NT	NT	0.5577
mineralization, vascular				
Overall Rates (a)	1/70 (1.43%)	0/55 (0.00%)	1/53 (1.89%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5495

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
kidneys				
nephropathy, chronic progressive				
Overall Rates (a)	68/70 (97.14%)	45/55 (81.82%)	44/53 (83.02%)	67/70 (95.71%)
Fisher's Exact Test; P-value		0.0051	0.0093	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8413
polyarteritis				
Overall Rates (a)	1/70 (1.43%)	0/55 (0.00%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2027
pyelitis				
Overall Rates (a)	11/70 (15.71%)	8/55 (14.55%)	3/53 (5.66%)	3/70 (4.29%)
Fisher's Exact Test; P-value		1.0000	0.0941	0.0454
Cochran-Armitage Trend Test; P-value		NT	0.1047	0.0099*
pyelonephritis, bilateral				
Overall Rates (a)	0/70 (0.00%)	1/55 (1.82%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4400	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6728

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
kidneys				
thrombus				
Overall Rates (a)	2/70 (2.86%)	1/55 (1.82%)	1/53 (1.89%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.2012
lacrimal glands, exorbital				
atrophy				
Overall Rates (a)	0/69 (0.00%)	1/49 (2.04%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.4153	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5604
depletion, secretory				
Overall Rates (a)	0/69 (0.00%)	1/49 (2.04%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4153	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6658
large intestine, cecum				
edema				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2073

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
large intestine, cecum				
inflammation				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4262	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6759
polyarteritis				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2073
large intestine, rectum				
inflammation, peritoneal				
Overall Rates (a)	0/70 (0.00%)	1/50 (2.00%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4167	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6708
larynx				
erosion/ulcer				
Overall Rates (a)	0/70 (0.00%)	0/49 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2087

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
larynx				
exudate, luminal				
Overall Rates (a)	0/70 (0.00%)	1/49 (2.04%)	1/52 (1.92%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.4118	0.4262	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4698
foreign material				
Overall Rates (a)	0/70 (0.00%)	2/49 (4.08%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.1675	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5460
inflammation				
Overall Rates (a)	0/70 (0.00%)	1/49 (2.04%)	0/52 (0.00%)	2/70 (2.86%)
Fisher's Exact Test; P-value		0.4118	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.2260
mucus increased				
Overall Rates (a)	0/70 (0.00%)	0/49 (0.00%)	2/52 (3.85%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	0.1797	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.0923

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
liver				
angiectasis				
Overall Rates (a)	2/70 (2.86%)	0/70 (0.00%)	1/70 (1.43%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.4964	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6530
congestion				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797
cyst, biliary, multiloculated				
Overall Rates (a)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547
cyst, biliary, simple				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
liver				
degeneration, cystic, focal				
Overall Rates (a)	24/70 (34.29%)	24/70 (34.29%)	19/70 (27.14%)	42/70 (60.00%)
Fisher's Exact Test; P-value		1.0000	0.4639	0.0038
Cochran-Armitage Trend Test; P-value		NT	0.3658	0.0073*
fibrosis				
Overall Rates (a)	0/70 (0.00%)	2/70 (2.86%)	0/70 (0.00%)	2/70 (2.86%)
Fisher's Exact Test; P-value		0.4964	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.3685
focus of cellular alteration, basophilic				
Overall Rates (a)	6/70 (8.57%)	5/70 (7.14%)	6/70 (8.57%)	13/70 (18.57%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.1372
Cochran-Armitage Trend Test; P-value		NT	NT	0.0577
focus of cellular alteration, clear				
Overall Rates (a)	2/70 (2.86%)	1/70 (1.43%)	2/70 (2.86%)	3/70 (4.29%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5218

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
liver				
focus of cellular alteration, eosinophilic				
Overall Rates (a)	15/70 (21.43%)	18/70 (25.71%)	6/70 (8.57%)	15/70 (21.43%)
Fisher's Exact Test; P-value		0.6909	0.0564	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4171
hematopoiesis, extramedullary				
Overall Rates (a)	19/70 (27.14%)	28/70 (40.00%)	24/70 (34.29%)	19/70 (27.14%)
Fisher's Exact Test; P-value		0.1519	0.4639	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8193
hyperplasia, bile duct				
Overall Rates (a)	40/70 (57.14%)	33/70 (47.14%)	32/70 (45.71%)	34/70 (48.57%)
Fisher's Exact Test; P-value		0.3101	0.2364	0.3973
Cochran-Armitage Trend Test; P-value		NT	NT	0.3107
hyperplasia, hepatocellular, regenerative				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
liver				
hypertrophy, hepatocyte, centrilobular				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	7/70 (10.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.0133
Cochran-Armitage Trend Test; P-value		NT	1.0000	0.0003*
infarct				
Overall Rates (a)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547
infiltration, mononuclear cell				
Overall Rates (a)	36/70 (51.43%)	28/70 (40.00%)	20/70 (28.57%)	25/70 (35.71%)
Fisher's Exact Test; P-value		0.2349	0.0094	0.0879
Cochran-Armitage Trend Test; P-value		0.1763	0.0059*	0.0249*
inflammation, acute				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
liver				
leukocytosis, sinusoidal				
Overall Rates (a)	0/70 (0.00%)	1/70 (1.43%)	1/70 (1.43%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	1.0000
macrophages, pigmented				
Overall Rates (a)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547
necrosis, focal				
Overall Rates (a)	6/70 (8.57%)	3/70 (4.29%)	4/70 (5.71%)	9/70 (12.86%)
Fisher's Exact Test; P-value		0.4932	0.7447	0.5861
Cochran-Armitage Trend Test; P-value		NT	NT	0.3214
necrosis, hepatocytes, centrilobular				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	1/70 (1.43%)	5/70 (7.14%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.2086
Cochran-Armitage Trend Test; P-value		NT	1.0000	0.0263*

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
liver				
osteosarcoma, malignant, secondary				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797
vacuolation, centrilobular				
Overall Rates (a)	4/70 (5.71%)	6/70 (8.57%)	2/70 (2.86%)	2/70 (2.86%)
Fisher's Exact Test; P-value		0.7447	0.6806	0.6806
Cochran-Armitage Trend Test; P-value		NT	NT	0.2209
vacuolation, diffuse				
Overall Rates (a)	3/70 (4.29%)	1/70 (1.43%)	1/70 (1.43%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.6195	0.6195	0.2446
Cochran-Armitage Trend Test; P-value		NT	NT	0.0698
vacuolation, focal				
Overall Rates (a)	9/70 (12.86%)	7/70 (10.00%)	5/70 (7.14%)	2/70 (2.86%)
Fisher's Exact Test; P-value		0.7914	0.3989	0.0552
Cochran-Armitage Trend Test; P-value		NT	0.2609	0.0254*

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
liver				
vacuolation, median cleft				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	2/70 (2.86%)	3/70 (4.29%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.6195
Cochran-Armitage Trend Test; P-value		NT	NT	0.1405
vacuolation, midzonal				
Overall Rates (a)	1/70 (1.43%)	2/70 (2.86%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1951
vacuolation, periportal				
Overall Rates (a)	18/70 (25.71%)	16/70 (22.86%)	16/70 (22.86%)	7/70 (10.00%)
Fisher's Exact Test; P-value		0.8440	0.8440	0.0259
Cochran-Armitage Trend Test; P-value		NT	0.6922	0.0288*
lung				
bacterial colonies				
Overall Rates (a)	3/70 (4.29%)	6/50 (12.00%)	6/53 (11.32%)	3/70 (4.29%)
Fisher's Exact Test; P-value		0.1614	0.1718	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9817

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
lung				
carcinoma, c-cell, malignant, secondary				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2034
carcinoma, cortical, malignant, secondary				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/53 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2071
crystals, hemoglobin				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	1/53 (1.89%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	0.4309	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2343
edema				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2034

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
lung				
foreign material				
Overall Rates (a)	0/70 (0.00%)	1/50 (2.00%)	0/53 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.4167	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5545
granuloma				
Overall Rates (a)	0/70 (0.00%)	1/50 (2.00%)	0/53 (0.00%)	2/70 (2.86%)
Fisher's Exact Test; P-value		0.4167	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.2244
hemangiosarcoma, malignant, secondary				
Overall Rates (a)	0/70 (0.00%)	1/50 (2.00%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4167	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6690
hemorrhage				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	3/53 (5.66%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	0.3139	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5758

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
lung				
histiocytosis, alveolar				
Overall Rates (a)	23/70 (32.86%)	15/50 (30.00%)	10/53 (18.87%)	26/70 (37.14%)
Fisher's Exact Test; P-value		0.8429	0.1017	0.7233
Cochran-Armitage Trend Test; P-value		NT	NT	0.8561
hyperplasia, bronchiolar-alveolar				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	1/53 (1.89%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4309	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6767
hyperplasia, type ii cell				
Overall Rates (a)	0/70 (0.00%)	1/50 (2.00%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4167	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6690
hypertrophy/hyperplasia, bronchiolar/bronchial				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	1/53 (1.89%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4309	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6767

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
lung				
inflammation, acute				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	0/53 (0.00%)	3/70 (4.29%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.6195
Cochran-Armitage Trend Test; P-value		NT	NT	0.2062
inflammation, perivascular				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	1/53 (1.89%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4309	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6767
inflammation, subacute/chronic				
Overall Rates (a)	2/70 (2.86%)	1/50 (2.00%)	3/53 (5.66%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	0.6509	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8606
leukocytosis, vascular				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	1/53 (1.89%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4309	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6767

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
lung				
macrophages, alveolar				
Overall Rates (a)	1/70 (1.43%)	1/50 (2.00%)	1/53 (1.89%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4572
macrophages, pigmented alveolar				
Overall Rates (a)	1/70 (1.43%)	2/50 (4.00%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.5700	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2176
metaplasia, osseous				
Overall Rates (a)	0/70 (0.00%)	1/50 (2.00%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4167	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6690
mucus increased				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	1/53 (1.89%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4309	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6767

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
lung				
necrosis				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/53 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2071
osteosarcoma, malignant, secondary				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2034
pneumonitis, uremic				
Overall Rates (a)	3/70 (4.29%)	0/50 (0.00%)	1/53 (1.89%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.2647	0.6334	0.2446
Cochran-Armitage Trend Test; P-value		NT	NT	0.0873
thrombus				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2034

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Diagnosis				
lymph node, axillary				
erythrocytosis/erythrophagocytosis, sinus				
Overall Rates (a)	1/12 (8.33%)	1/5 (20.00%)	0/6 (0.00%)	0/8 (0.00%)
Fisher's Exact Test; P-value		0.5147	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.3354
histiocytosis, sinus				
Overall Rates (a)	1/12 (8.33%)	0/5 (0.00%)	0/6 (0.00%)	0/8 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2816
hyperplasia, lymphoid, generalized				
Overall Rates (a)	0/12 (0.00%)	0/5 (0.00%)	0/6 (0.00%)	1/8 (12.50%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1721
lymph node, mandibular				
dilatation, sinus				
Overall Rates (a)	4/70 (5.71%)	2/49 (4.08%)	4/53 (7.55%)	2/69 (2.90%)
Fisher's Exact Test; P-value		1.0000	0.7247	0.6806
Cochran-Armitage Trend Test; P-value		NT	NT	0.6135

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
lymph node, mandibular				
erythrocytosis/erythrophagocytosis, sinus				
Overall Rates (a)	7/70 (10.00%)	6/49 (12.24%)	3/53 (5.66%)	11/69 (15.94%)
Fisher's Exact Test; P-value		0.7695	0.5126	0.3238
Cochran-Armitage Trend Test; P-value		NT	NT	0.4446
hemorrhage				
Overall Rates (a)	1/70 (1.43%)	0/49 (0.00%)	0/53 (0.00%)	0/69 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2048
hyperplasia, lymphocyte/plasmacyte, medulla				
Overall Rates (a)	1/70 (1.43%)	1/49 (2.04%)	0/53 (0.00%)	0/69 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2306
osteosarcoma, malignant, secondary				
Overall Rates (a)	1/70 (1.43%)	0/49 (0.00%)	0/53 (0.00%)	0/69 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2048

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
lymph node, mediastinal				
dilatation, sinus				
Overall Rates (a)	0/3 (0.00%)	1/1 (100.00%)	1/3 (33.33%)	0/3 (0.00%)
Fisher's Exact Test; P-value		0.2500	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9005
lymph node, mesenteric				
depletion, lymphoid, generalized				
Overall Rates (a)	0/70 (0.00%)	0/51 (0.00%)	0/54 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2056
dilatation, sinus				
Overall Rates (a)	3/70 (4.29%)	2/51 (3.92%)	1/54 (1.85%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	0.6316	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5334
erythrocytosis/erythrophagocytosis, sinus				
Overall Rates (a)	5/70 (7.14%)	1/51 (1.96%)	1/54 (1.85%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.3992	0.2311	0.2086
Cochran-Armitage Trend Test; P-value		NT	NT	0.0660

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
lymph node, mesenteric				
inflammation, granulomatous				
Overall Rates (a)	0/70 (0.00%)	1/51 (1.96%)	0/54 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4215	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6680
nerve, sciatic				
degeneration, axonal/myelin				
Overall Rates (a)	49/70 (70.00%)	31/50 (62.00%)	22/52 (42.31%)	42/70 (60.00%)
Fisher's Exact Test; P-value		0.4331	0.0029	0.2877
Cochran-Armitage Trend Test; P-value		NT	NT	0.0858
nose, level a				
exudate, nasal passage				
Overall Rates (a)	9/70 (12.86%)	0/50 (0.00%)	2/52 (3.85%)	5/70 (7.14%)
Fisher's Exact Test; P-value		0.0101	0.1142	0.3989
Cochran-Armitage Trend Test; P-value		NT	NT	0.2702
fibrous osteodystrophy				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5470

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
nose, level a				
foreign material				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	2/52 (3.85%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.5747	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8022
fungus/yeast				
Overall Rates (a)	4/70 (5.71%)	0/50 (0.00%)	1/52 (1.92%)	2/70 (2.86%)
Fisher's Exact Test; P-value		0.1397	0.3924	0.6806
Cochran-Armitage Trend Test; P-value		NT	NT	0.4145
inflammation				
Overall Rates (a)	7/70 (10.00%)	2/50 (4.00%)	1/52 (1.92%)	4/70 (5.71%)
Fisher's Exact Test; P-value		0.3019	0.1361	0.5319
Cochran-Armitage Trend Test; P-value		NT	NT	0.2413
metaplasia, squamous				
Overall Rates (a)	2/70 (2.86%)	0/50 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.5098	0.5068	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4598

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
nose, level b				
erosion/ulcer				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2048
exudate, nasal passage				
Overall Rates (a)	13/70 (18.57%)	1/50 (2.00%)	4/52 (7.69%)	3/70 (4.29%)
Fisher's Exact Test; P-value		0.0074	0.1142	0.0146
Cochran-Armitage Trend Test; P-value		0.0055*	0.0344*	0.0090*
fibrous osteodystrophy				
Overall Rates (a)	2/70 (2.86%)	0/50 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.5098	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.2195
foreign material				
Overall Rates (a)	2/70 (2.86%)	1/50 (2.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.2007

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
nose, level b				
fungus/yeast				
Overall Rates (a)	7/70 (10.00%)	0/50 (0.00%)	3/52 (5.77%)	2/70 (2.86%)
Fisher's Exact Test; P-value		0.0405	0.5142	0.1654
Cochran-Armitage Trend Test; P-value		NT	NT	0.1318
inflammation				
Overall Rates (a)	9/70 (12.86%)	0/50 (0.00%)	1/52 (1.92%)	2/70 (2.86%)
Fisher's Exact Test; P-value		0.0101	0.0426	0.0552
Cochran-Armitage Trend Test; P-value		0.0087*	0.0069*	0.0123*
inflammation, acute				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4262	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6759
metaplasia, squamous				
Overall Rates (a)	4/70 (5.71%)	0/50 (0.00%)	1/52 (1.92%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.1397	0.3924	0.3659
Cochran-Armitage Trend Test; P-value		NT	NT	0.1616

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
nose, level b				
odontodysplasia				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2048
nose, level c				
erosion/ulcer				
Overall Rates (a)	3/70 (4.29%)	0/50 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.2647	0.6354	0.2446
Cochran-Armitage Trend Test; P-value		NT	NT	0.0884
exudate, nasal passage				
Overall Rates (a)	8/70 (11.43%)	1/50 (2.00%)	4/52 (7.69%)	3/70 (4.29%)
Fisher's Exact Test; P-value		0.0783	0.5543	0.2076
Cochran-Armitage Trend Test; P-value		NT	NT	0.1868
fibrous osteodystrophy				
Overall Rates (a)	3/70 (4.29%)	0/50 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.2647	0.6354	0.2446
Cochran-Armitage Trend Test; P-value		NT	NT	0.0884

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
nose, level c				
foreign material				
Overall Rates (a)	1/70 (1.43%)	1/50 (2.00%)	3/52 (5.77%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	0.3113	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.7345
fungus/yeast				
Overall Rates (a)	5/70 (7.14%)	0/50 (0.00%)	2/52 (3.85%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.0746	0.6975	0.2086
Cochran-Armitage Trend Test; P-value		NT	NT	0.1279
inflammation				
Overall Rates (a)	6/70 (8.57%)	0/50 (0.00%)	1/52 (1.92%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.0402	0.2367	0.1156
Cochran-Armitage Trend Test; P-value		0.0344*	0.0494*	0.0334*
inflammation, acute				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4262	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6759

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
nose, level c				
metaplasia, squamous				
Overall Rates (a)	7/70 (10.00%)	0/50 (0.00%)	2/52 (3.85%)	2/70 (2.86%)
Fisher's Exact Test; P-value		0.0405	0.2984	0.1654
Cochran-Armitage Trend Test; P-value		NT	NT	0.0892
nose, level d				
erosion/ulcer				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	1/52 (1.92%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8116
exudate, nasal passage				
Overall Rates (a)	5/70 (7.14%)	1/50 (2.00%)	3/52 (5.77%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.3988	1.0000	0.0581
Cochran-Armitage Trend Test; P-value		NT	NT	0.0617
fibrous osteodystrophy				
Overall Rates (a)	3/70 (4.29%)	0/50 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.2647	0.6354	0.2446
Cochran-Armitage Trend Test; P-value		NT	NT	0.0884

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
nose, level d				
foreign material				
Overall Rates (a)	0/70 (0.00%)	1/50 (2.00%)	3/52 (5.77%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4167	0.0749	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6766
fungus/yeast				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2048
inflammation				
Overall Rates (a)	2/70 (2.86%)	0/50 (0.00%)	2/52 (3.85%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.5098	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8431
inflammation, acute				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4262	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6759

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
nose, level d				
metaplasia, squamous				
Overall Rates (a)	3/70 (4.29%)	0/50 (0.00%)	1/52 (1.92%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.2647	0.6354	0.6195
Cochran-Armitage Trend Test; P-value		NT	NT	0.3379
pancreas				
atrophy, acinar				
Overall Rates (a)	17/70 (24.29%)	17/70 (24.29%)	17/70 (24.29%)	12/70 (17.14%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4045
Cochran-Armitage Trend Test; P-value		NT	NT	0.3379
fibrosis				
Overall Rates (a)	21/70 (30.00%)	14/70 (20.00%)	21/70 (30.00%)	18/70 (25.71%)
Fisher's Exact Test; P-value		0.2414	1.0000	0.7064
Cochran-Armitage Trend Test; P-value		NT	NT	0.9037
hyperplasia, acinar cell, focal				
Overall Rates (a)	16/70 (22.86%)	18/70 (25.71%)	7/70 (10.00%)	21/70 (30.00%)
Fisher's Exact Test; P-value		0.8440	0.0664	0.4436
Cochran-Armitage Trend Test; P-value		NT	NT	0.7972

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
pancreas				
hyperplasia, islet cell				
Overall Rates (a)	2/70 (2.86%)	0/70 (0.00%)	2/70 (2.86%)	3/70 (4.29%)
Fisher's Exact Test; P-value		0.4964	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.3929
inflammation, acute				
Overall Rates (a)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547
mineralization, vascular				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547
polyarteritis				
Overall Rates (a)	2/70 (2.86%)	2/70 (2.86%)	2/70 (2.86%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.2690

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
parathyroid glands				
carcinoma, c-cell, malignant, secondary				
Overall Rates (a)	0/64 (0.00%)	0/43 (0.00%)	0/46 (0.00%)	1/60 (1.67%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4839
Cochran-Armitage Trend Test; P-value		NT	NT	0.2008
hyperplasia, diffuse				
Overall Rates (a)	1/64 (1.56%)	0/43 (0.00%)	2/46 (4.35%)	0/60 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.5703	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8313
hyperplasia, focal				
Overall Rates (a)	5/64 (7.81%)	1/43 (2.33%)	1/46 (2.17%)	6/60 (10.00%)
Fisher's Exact Test; P-value		0.3980	0.3977	0.7579
Cochran-Armitage Trend Test; P-value		NT	NT	0.6700
pharynx				
hemorrhage				
Overall Rates (a)	0/70 (0.00%)	0/49 (0.00%)	0/52 (0.00%)	1/69 (1.45%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.2062

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
pharynx				
hyperplasia, squamous epithelium				
Overall Rates (a)	0/70 (0.00%)	0/49 (0.00%)	0/52 (0.00%)	1/69 (1.45%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.2062
inflammation				
Overall Rates (a)	0/70 (0.00%)	0/49 (0.00%)	0/52 (0.00%)	2/69 (2.90%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.2446
Cochran-Armitage Trend Test; P-value		NT	NT	0.0732
pituitary gland				
cyst				
Overall Rates (a)	4/70 (5.71%)	4/52 (7.69%)	0/60 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.7222	0.1237	0.3659
Cochran-Armitage Trend Test; P-value		NT	NT	0.0537
fibrosis				
Overall Rates (a)	0/70 (0.00%)	0/52 (0.00%)	1/60 (1.67%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4615	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6781

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
pituitary gland				
hyperplasia, craniopharyngeal				
Overall Rates (a)	0/70 (0.00%)	0/52 (0.00%)	0/60 (0.00%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.0714
hyperplasia, focal, pars distalis				
Overall Rates (a)	6/70 (8.57%)	4/52 (7.69%)	3/60 (5.00%)	3/70 (4.29%)
Fisher's Exact Test; P-value		1.0000	0.5045	0.4932
Cochran-Armitage Trend Test; P-value		NT	NT	0.2456
macrophages, pigmented				
Overall Rates (a)	0/70 (0.00%)	0/52 (0.00%)	1/60 (1.67%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4615	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6781
schwannoma, malignant, secondary				
Overall Rates (a)	0/70 (0.00%)	0/52 (0.00%)	0/60 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2033

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
prostate gland				
abscess				
Overall Rates (a)	0/70 (0.00%)	0/51 (0.00%)	1/53 (1.89%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4309	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6749
inflammation, acute				
Overall Rates (a)	4/70 (5.71%)	4/51 (7.84%)	4/53 (7.55%)	2/70 (2.86%)
Fisher's Exact Test; P-value		0.7199	0.7247	0.6806
Cochran-Armitage Trend Test; P-value		NT	NT	0.4774
inflammation, chronic-active				
Overall Rates (a)	12/70 (17.14%)	2/51 (3.92%)	1/53 (1.89%)	10/70 (14.29%)
Fisher's Exact Test; P-value		0.0408	0.0066	0.8169
Cochran-Armitage Trend Test; P-value		NT	NT	0.5209
inflammation, subacute/chronic				
Overall Rates (a)	3/70 (4.29%)	2/51 (3.92%)	1/53 (1.89%)	3/70 (4.29%)
Fisher's Exact Test; P-value		1.0000	0.6334	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8777

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
salivary gland, mandibular				
depletion, secretory				
Overall Rates (a)	1/70 (1.43%)	0/49 (0.00%)	0/52 (0.00%)	0/69 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2062
fibrosis				
Overall Rates (a)	0/70 (0.00%)	0/49 (0.00%)	0/52 (0.00%)	1/69 (1.45%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.2062
mineralization, vascular				
Overall Rates (a)	0/70 (0.00%)	0/49 (0.00%)	1/52 (1.92%)	0/69 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4262	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6735
salivary gland, parotid				
atrophy				
Overall Rates (a)	1/70 (1.43%)	2/49 (4.08%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.5678	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2191

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
salivary gland, sublingual				
depletion, secretory				
Overall Rates (a)	1/69 (1.45%)	0/49 (0.00%)	0/52 (0.00%)	0/68 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2051
seminal vesicles				
depletion, secretory				
Overall Rates (a)	5/70 (7.14%)	3/50 (6.00%)	5/53 (9.43%)	6/70 (8.57%)
Fisher's Exact Test; P-value		1.0000	0.7441	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6314
dilatation				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	1/53 (1.89%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4013
inflammation				
Overall Rates (a)	8/70 (11.43%)	5/50 (10.00%)	2/53 (3.77%)	3/70 (4.29%)
Fisher's Exact Test; P-value		1.0000	0.1850	0.2076
Cochran-Armitage Trend Test; P-value		NT	NT	0.0600

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
skeletal muscle, biceps femoris				
atrophy				
Overall Rates (a)	2/70 (2.86%)	1/50 (2.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.2007
degeneration/necrosis, myofiber				
Overall Rates (a)	18/70 (25.71%)	8/50 (16.00%)	5/52 (9.62%)	20/70 (28.57%)
Fisher's Exact Test; P-value		0.2627	0.0342	0.8495
Cochran-Armitage Trend Test; P-value		NT	NT	0.8643
degeneration/regeneration, myofiber				
Overall Rates (a)	2/70 (2.86%)	1/50 (2.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	0.5068	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.3924
skin/skin, subcutis				
abscess				
Overall Rates (a)	2/70 (2.86%)	0/58 (0.00%)	1/59 (1.69%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.5005	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.2095

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
skin/skin, subcutis				
alopecia/hypotrichosis				
Overall Rates (a)	1/70 (1.43%)	1/58 (1.72%)	0/59 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2199
crust, serocellular				
Overall Rates (a)	0/70 (0.00%)	2/58 (3.45%)	0/59 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.2034	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5389
cyst, keratin				
Overall Rates (a)	0/70 (0.00%)	0/58 (0.00%)	1/59 (1.69%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4574	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6670
erosion/ulcer				
Overall Rates (a)	1/70 (1.43%)	2/58 (3.45%)	2/59 (3.39%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.5897	0.5923	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5565

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
skin/skin, subcutis				
hyperkeratosis				
Overall Rates (a)	1/70 (1.43%)	0/58 (0.00%)	0/59 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1944
hyperplasia, epidermal				
Overall Rates (a)	1/70 (1.43%)	2/58 (3.45%)	1/59 (1.69%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.5897	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8426
inflammation				
Overall Rates (a)	0/70 (0.00%)	1/58 (1.72%)	0/59 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4531	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6645
osteosarcoma, malignant, secondary				
Overall Rates (a)	1/70 (1.43%)	0/58 (0.00%)	0/59 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1944

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
small intestine, duodenum				
hyperplasia, mucosal				
Overall Rates (a)	0/70 (0.00%)	1/50 (2.00%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4167	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6708
small intestine, ileum				
dilatation, gland/lumen				
Overall Rates (a)	1/70 (1.43%)	0/51 (0.00%)	0/53 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9961
diverticulum				
Overall Rates (a)	1/70 (1.43%)	0/51 (0.00%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2033
small intestine, jejunum				
dilatation, gland/lumen				
Overall Rates (a)	1/70 (1.43%)	1/51 (1.96%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2304

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
small intestine, jejunum				
erosion/ulcer				
Overall Rates (a)	0/70 (0.00%)	1/51 (1.96%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4215	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6716
lymphangiectasis				
Overall Rates (a)	0/70 (0.00%)	1/51 (1.96%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4215	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6716
spinal cord, thoracic				
degeneration, axonal/myelin				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2073
spleen				
cyst, capsule				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2048

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
spleen				
depletion, lymphoid, generalized				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2073
hematopoiesis, extramedullary, increased				
Overall Rates (a)	26/70 (37.14%)	15/50 (30.00%)	16/52 (30.77%)	23/70 (32.86%)
Fisher's Exact Test; P-value		0.4417	0.5640	0.7233
Cochran-Armitage Trend Test; P-value		NT	NT	0.6186
hyperplasia, reactive red pulp/stromal				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2073
inflammation, peritoneal				
Overall Rates (a)	0/70 (0.00%)	1/50 (2.00%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4167	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6708

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
stomach, glandular				
erosion/ulcer				
Overall Rates (a)	0/70 (0.00%)	2/50 (4.00%)	3/53 (5.66%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.1716	0.0774	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4941
gastropathy, uremic				
Overall Rates (a)	4/70 (5.71%)	1/50 (2.00%)	2/53 (3.77%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.3998	0.6982	0.1196
Cochran-Armitage Trend Test; P-value		NT	NT	0.0732
hyperplasia, mucosal				
Overall Rates (a)	0/70 (0.00%)	1/50 (2.00%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4167	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6690
inflammation				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	1/53 (1.89%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4309	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6767

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
stomach, nonglandular				
cyst, keratin				
Overall Rates (a)	0/70 (0.00%)	0/51 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2059
erosion/ulcer				
Overall Rates (a)	5/70 (7.14%)	4/51 (7.84%)	5/52 (9.62%)	5/70 (7.14%)
Fisher's Exact Test; P-value		1.0000	0.7424	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9261
gastropathy, uremic				
Overall Rates (a)	0/70 (0.00%)	0/51 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4262	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6741
hyperplasia, epithelial, limiting ridge				
Overall Rates (a)	0/70 (0.00%)	1/51 (1.96%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4215	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6716

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
stomach, nonglandular				
hyperplasia, epithelial, nonglandular				
Overall Rates (a)	6/70 (8.57%)	3/51 (5.88%)	4/52 (7.69%)	8/70 (11.43%)
Fisher's Exact Test; P-value		0.7323	1.0000	0.7792
Cochran-Armitage Trend Test; P-value		NT	NT	0.5060
inflammation				
Overall Rates (a)	7/70 (10.00%)	3/51 (5.88%)	5/52 (9.62%)	7/70 (10.00%)
Fisher's Exact Test; P-value		0.5163	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8573
testes				
degeneration/atrophy, seminiferous tubules, bilateral				
Overall Rates (a)	7/70 (10.00%)	4/70 (5.71%)	5/70 (7.14%)	3/70 (4.29%)
Fisher's Exact Test; P-value		0.5319	0.7641	0.3255
Cochran-Armitage Trend Test; P-value		NT	NT	0.2433
degeneration/atrophy, seminiferous tubules, unilateral				
Overall Rates (a)	3/70 (4.29%)	3/70 (4.29%)	1/70 (1.43%)	4/70 (5.71%)
Fisher's Exact Test; P-value		1.0000	0.6195	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8908

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
testes				
dilatation, seminiferous tubules, bilateral				
Overall Rates (a)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547
dilatation, seminiferous tubules, unilateral				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	2/70 (2.86%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4964	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5263
edema				
Overall Rates (a)	1/70 (1.43%)	1/70 (1.43%)	1/70 (1.43%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4369
granuloma, spermatic				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
testes				
hyperplasia, interstitial cell				
Overall Rates (a)	7/70 (10.00%)	7/70 (10.00%)	3/70 (4.29%)	15/70 (21.43%)
Fisher's Exact Test; P-value		1.0000	0.3255	0.1025
Cochran-Armitage Trend Test; P-value		NT	NT	0.0935
inflammation, peritoneal				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797
mesothelioma, malignant, secondary				
Overall Rates (a)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547
polyarteritis				
Overall Rates (a)	6/70 (8.57%)	5/70 (7.14%)	7/70 (10.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.1156
Cochran-Armitage Trend Test; P-value		NT	NT	0.1679

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
thymus				
depletion, lymphoid, generalized				
Overall Rates (a)	67/69 (97.10%)	46/50 (92.00%)	49/52 (94.23%)	68/68 (100.00%)
Fisher's Exact Test; P-value		0.2370	0.6505	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.3178
hyperplasia, epithelial cell				
Overall Rates (a)	0/69 (0.00%)	1/50 (2.00%)	0/52 (0.00%)	0/68 (0.00%)
Fisher's Exact Test; P-value		0.4202	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6735
hyperplasia, lymphoid, medulla				
Overall Rates (a)	0/69 (0.00%)	1/50 (2.00%)	0/52 (0.00%)	0/68 (0.00%)
Fisher's Exact Test; P-value		0.4202	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6735
thyroid gland				
cyst, follicular				
Overall Rates (a)	0/70 (0.00%)	2/51 (3.92%)	1/53 (1.89%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.1756	0.4309	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8016

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
thyroid gland				
hyperplasia, c-cell, focal				
Overall Rates (a)	9/70 (12.86%)	3/51 (5.88%)	3/53 (5.66%)	3/70 (4.29%)
Fisher's Exact Test; P-value		0.2363	0.2297	0.1284
Cochran-Armitage Trend Test; P-value		NT	NT	0.0607
hyperplasia, follicular cell				
Overall Rates (a)	1/70 (1.43%)	0/51 (0.00%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2033
hypertrophy/hyperplasia, follicular cell				
Overall Rates (a)	0/70 (0.00%)	1/51 (1.96%)	0/53 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.4215	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5522
inflammation, subacute/chronic				
Overall Rates (a)	0/70 (0.00%)	1/51 (1.96%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4215	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6698

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
tongue				
hyperplasia, squamous cell				
Overall Rates (a)	0/70 (0.00%)	0/69 (0.00%)	0/70 (0.00%)	2/69 (2.90%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.2446
Cochran-Armitage Trend Test; P-value		NT	NT	0.0567
inflammation, subacute/chronic				
Overall Rates (a)	1/70 (1.43%)	0/69 (0.00%)	0/70 (0.00%)	2/69 (2.90%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.6195
Cochran-Armitage Trend Test; P-value		NT	NT	0.4336
mineralization, vascular				
Overall Rates (a)	0/70 (0.00%)	0/69 (0.00%)	1/70 (1.43%)	0/69 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6524
trachea				
bacterial colonies				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4262	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6759

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
trachea				
exudate, luminal				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2073
inflammation, acute				
Overall Rates (a)	1/70 (1.43%)	0/50 (0.00%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2048
ureters				
crystals, hemoglobin				
Overall Rates (a)	1/70 (1.43%)	0/51 (0.00%)	0/52 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2046
dilatation				
Overall Rates (a)	5/70 (7.14%)	2/51 (3.92%)	5/52 (9.62%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.6976	0.7424	0.2086
Cochran-Armitage Trend Test; P-value		NT	NT	0.2768

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
ureters				
hemorrhage				
Overall Rates (a)	0/70 (0.00%)	0/51 (0.00%)	1/52 (1.92%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4262	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6741
inflammation				
Overall Rates (a)	0/70 (0.00%)	0/51 (0.00%)	0/52 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2059
urinary bladder				
bacterial colonies				
Overall Rates (a)	0/70 (0.00%)	0/52 (0.00%)	0/53 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2044
calculus/calculi				
Overall Rates (a)	0/70 (0.00%)	2/52 (3.85%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.1797	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5466

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
urinary bladder				
dilatation				
Overall Rates (a)	2/70 (2.86%)	1/52 (1.92%)	4/53 (7.55%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	0.4009	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6705
erosion/ulcer				
Overall Rates (a)	1/70 (1.43%)	0/52 (0.00%)	0/53 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2031
hemorrhage				
Overall Rates (a)	2/70 (2.86%)	0/52 (0.00%)	3/53 (5.66%)	2/70 (2.86%)
Fisher's Exact Test; P-value		0.5068	0.6509	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6300
hyperplasia, papillary/nodular transitional cell				
Overall Rates (a)	1/70 (1.43%)	2/52 (3.85%)	0/53 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.5747	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6674

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - MALE

Tissue Diagnosis	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
urinary bladder				
hyperplasia, simple transitional cell				
Overall Rates (a)	3/70 (4.29%)	3/52 (5.77%)	6/53 (11.32%)	2/70 (2.86%)
Fisher's Exact Test; P-value		0.6992	0.1718	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9947
inflammation				
Overall Rates (a)	6/70 (8.57%)	6/52 (11.54%)	6/53 (11.32%)	4/70 (5.71%)
Fisher's Exact Test; P-value		0.7600	0.7608	0.7447
Cochran-Armitage Trend Test; P-value		NT	NT	0.5650
inflammation, acute				
Overall Rates (a)	0/70 (0.00%)	0/52 (0.00%)	1/53 (1.89%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4309	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6731
inflammation, peritoneal				
Overall Rates (a)	0/70 (0.00%)	1/52 (1.92%)	1/53 (1.89%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4262	0.4309	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9980

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
adrenal glands				
angiectasis/cystic degeneration, focal cortical				
Overall Rates (a)	64/70 (91.43%)	64/70 (91.43%)	61/70 (87.14%)	60/70 (85.71%)
Fisher's Exact Test; P-value		1.0000	0.5861	0.4264
Cochran-Armitage Trend Test; P-value		NT	NT	0.2022
atrophy, cortical				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	2/70 (2.86%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.3138
hematopoiesis, extramedullary				
Overall Rates (a)	1/70 (1.43%)	1/70 (1.43%)	3/70 (4.29%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	0.6195	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.7125
hyperplasia, focal cortical				
Overall Rates (a)	8/70 (11.43%)	15/70 (21.43%)	10/70 (14.29%)	3/70 (4.29%)
Fisher's Exact Test; P-value		0.1703	0.8014	0.2076
Cochran-Armitage Trend Test; P-value		NT	NT	0.1109

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
adrenal glands				
hyperplasia, focal medullary				
Overall Rates (a)	6/70 (8.57%)	8/70 (11.43%)	8/70 (11.43%)	10/70 (14.29%)
Fisher's Exact Test; P-value		0.7792	0.7792	0.4264
Cochran-Armitage Trend Test; P-value		NT	NT	0.3143
hypertrophy, focal cortical				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547
vacuolation, focal				
Overall Rates (a)	2/70 (2.86%)	1/70 (1.43%)	1/70 (1.43%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	1.0000
aorta				
mineralization				
Overall Rates (a)	1/70 (1.43%)	0/48 (0.00%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2009

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
bone marrow, femur				
bacterial colonies				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
hyperplasia, granulocytic				
Overall Rates (a)	13/70 (18.57%)	14/48 (29.17%)	5/55 (9.09%)	15/70 (21.43%)
Fisher's Exact Test; P-value		0.1893	0.1991	0.8330
Cochran-Armitage Trend Test; P-value		NT	NT	0.7657
hyperplasia, mixed				
Overall Rates (a)	2/70 (2.86%)	0/48 (0.00%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.5133	0.5032	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.0699
bone marrow, sternum				
angiectasis				
Overall Rates (a)	1/70 (1.43%)	0/48 (0.00%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2009

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
bone marrow, sternum				
hyperplasia, granulocytic				
Overall Rates (a)	11/70 (15.71%)	10/48 (20.83%)	5/55 (9.09%)	6/70 (8.57%)
Fisher's Exact Test; P-value		0.4756	0.2970	0.3007
Cochran-Armitage Trend Test; P-value		NT	NT	0.0944
hyperplasia, mixed				
Overall Rates (a)	1/70 (1.43%)	0/48 (0.00%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2009
proliferation, fibro-osseous				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
bone, femur				
hyperostosis				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
bone, sternum				
hyperostosis				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
brain				
bacterial colonies				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
carcinoma, pars distalis, malignant, secondary				
Overall Rates (a)	5/70 (7.14%)	3/48 (6.25%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.0664	0.0581
Cochran-Armitage Trend Test; P-value		NT	0.0660	0.0057*
compression, ventral (pituitary tumor)				
Overall Rates (a)	32/70 (45.71%)	31/48 (64.58%)	35/55 (63.64%)	19/70 (27.14%)
Fisher's Exact Test; P-value		0.0601	0.0498	0.0346
Cochran-Armitage Trend Test; P-value		0.0444*	0.0375*	0.0379*

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
brain				
hemorrhage				
Overall Rates (a)	2/70 (2.86%)	5/48 (10.42%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.1189	0.5032	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.0702
inflammation, embolic				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
eyes				
cataract				
Overall Rates (a)	0/69 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	3/70 (4.29%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.2446
Cochran-Armitage Trend Test; P-value		NT	1.0000	0.0296*
inflammation, acute				
Overall Rates (a)	0/69 (0.00%)	0/48 (0.00%)	1/55 (1.82%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4435	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6852

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
eyes, retina				
degeneration/atrophy, retina, bilateral				
Overall Rates (a)	1/62 (1.61%)	2/43 (4.65%)	1/53 (1.89%)	0/65 (0.00%)
Fisher's Exact Test; P-value		0.5662	1.0000	0.4882
Cochran-Armitage Trend Test; P-value		NT	NT	0.3536
degeneration/atrophy, retina, unilateral				
Overall Rates (a)	0/62 (0.00%)	3/43 (6.98%)	2/53 (3.77%)	2/65 (3.08%)
Fisher's Exact Test; P-value		0.0658	0.2102	0.4963
Cochran-Armitage Trend Test; P-value		NT	NT	0.4738
detachment, retinal				
Overall Rates (a)	0/62 (0.00%)	0/43 (0.00%)	0/53 (0.00%)	1/65 (1.54%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2159
fold/rosette, retinal				
Overall Rates (a)	0/62 (0.00%)	1/43 (2.33%)	0/53 (0.00%)	0/65 (0.00%)
Fisher's Exact Test; P-value		0.4095	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6450

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
harderian glands				
hyperplasia, focal				
Overall Rates (a)	6/69 (8.70%)	1/48 (2.08%)	2/55 (3.64%)	2/69 (2.90%)
Fisher's Exact Test; P-value		0.2373	0.2988	0.2744
Cochran-Armitage Trend Test; P-value		NT	NT	0.1400
heart				
bacterial colonies				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
cardiomyopathy				
Overall Rates (a)	39/70 (55.71%)	27/48 (56.25%)	23/55 (41.82%)	35/70 (50.00%)
Fisher's Exact Test; P-value		1.0000	0.1504	0.6117
Cochran-Armitage Trend Test; P-value		NT	NT	0.2899
inflammation				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
heart				
thrombus				
Overall Rates (a)	0/70 (0.00%)	1/48 (2.08%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.4068	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5611
kidneys				
adenocarcinoma, malignant, secondary				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797
bacterial colonies				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797
cyst				
Overall Rates (a)	1/70 (1.43%)	2/70 (2.86%)	1/70 (1.43%)	4/70 (5.71%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.3659
Cochran-Armitage Trend Test; P-value		NT	NT	0.2002

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
kidneys				
dilatation, tubular				
Overall Rates (a)	4/70 (5.71%)	2/70 (2.86%)	5/70 (7.14%)	28/70 (40.00%)
Fisher's Exact Test; P-value		0.6806	1.0000	0.0000
Cochran-Armitage Trend Test; P-value		NT	0.7051	0.0000*
edema, papilla				
Overall Rates (a)	4/70 (5.71%)	1/70 (1.43%)	2/70 (2.86%)	43/70 (61.43%)
Fisher's Exact Test; P-value		0.3659	0.6806	0.0000
Cochran-Armitage Trend Test; P-value		NT	0.3475	0.0000*
fibrosis				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797
hyaline, droplets, increased				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	2/70 (2.86%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4964	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5263

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
kidneys				
hydronephrosis, bilateral				
Overall Rates (a)	1/70 (1.43%)	2/70 (2.86%)	0/70 (0.00%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8403
hydronephrosis, unilateral				
Overall Rates (a)	5/70 (7.14%)	2/70 (2.86%)	2/70 (2.86%)	4/70 (5.71%)
Fisher's Exact Test; P-value		0.4411	0.4411	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.7037
hyperplasia, transitional cell				
Overall Rates (a)	6/70 (8.57%)	3/70 (4.29%)	12/70 (17.14%)	33/70 (47.14%)
Fisher's Exact Test; P-value		0.4932	0.2060	0.0000
Cochran-Armitage Trend Test; P-value		NT	0.0917	0.0000*
hyperplasia, tubular				
Overall Rates (a)	0/70 (0.00%)	2/70 (2.86%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4964	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5263

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
kidneys				
infarct				
Overall Rates (a)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547
inflammation, acute				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797
inflammation, embolic				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797
macrophages, pigmented				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
kidneys				
mineralization, pelvic				
Overall Rates (a)	52/70 (74.29%)	63/70 (90.00%)	58/70 (82.86%)	63/70 (90.00%)
Fisher's Exact Test; P-value		0.0259	0.3031	0.0259
Cochran-Armitage Trend Test; P-value		NT	0.1842	0.0401*
mineralization, tubular				
Overall Rates (a)	25/70 (35.71%)	32/70 (45.71%)	28/70 (40.00%)	42/70 (60.00%)
Fisher's Exact Test; P-value		0.3020	0.7277	0.0066
Cochran-Armitage Trend Test; P-value		NT	0.6063	0.0118*
necrosis, papillary				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	16/70 (22.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.0000
Cochran-Armitage Trend Test; P-value		NT	1.0000	0.0000*
nephropathy, chronic progressive				
Overall Rates (a)	39/70 (55.71%)	40/70 (57.14%)	41/70 (58.57%)	64/70 (91.43%)
Fisher's Exact Test; P-value		1.0000	0.8645	0.0000
Cochran-Armitage Trend Test; P-value		NT	0.7333	0.0000*

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
kidneys				
polyarteritis				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547
pyelitis				
Overall Rates (a)	11/70 (15.71%)	10/70 (14.29%)	15/70 (21.43%)	4/70 (5.71%)
Fisher's Exact Test; P-value		1.0000	0.5150	0.0986
Cochran-Armitage Trend Test; P-value		NT	NT	0.2225
lacrimal glands, exorbital				
atrophy				
Overall Rates (a)	0/69 (0.00%)	1/48 (2.08%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4103	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6597
depletion, secretory				
Overall Rates (a)	0/69 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2109

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
large intestine, cecum				
erosion/ulcer				
Overall Rates (a)	1/70 (1.43%)	1/48 (2.08%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2247
hypertrophy/hyperplasia, goblet cell				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
polyarteritis				
Overall Rates (a)	2/70 (2.86%)	0/48 (0.00%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.5133	0.5032	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.0699
large intestine, colon				
hypertrophy/hyperplasia, goblet cell				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
large intestine, rectum				
hypertrophy/hyperplasia, goblet cell				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
larynx				
exudate, luminal				
Overall Rates (a)	0/69 (0.00%)	0/48 (0.00%)	1/55 (1.82%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4435	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6852
foreign material				
Overall Rates (a)	0/69 (0.00%)	1/48 (2.08%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4103	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6597
inflammation				
Overall Rates (a)	0/69 (0.00%)	0/48 (0.00%)	2/55 (3.64%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.1947	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5657

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
larynx				
mucus increased				
Overall Rates (a)	0/69 (0.00%)	1/48 (2.08%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4103	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6597
liver				
angiectasis				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	3/70 (4.29%)	5/70 (7.14%)
Fisher's Exact Test; P-value		1.0000	0.6195	0.2086
Cochran-Armitage Trend Test; P-value		NT	0.2173	0.0233*
cyst, biliary, simple				
Overall Rates (a)	2/70 (2.86%)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4964	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.0697
degeneration, cystic, focal				
Overall Rates (a)	2/70 (2.86%)	2/70 (2.86%)	2/70 (2.86%)	14/70 (20.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.0024
Cochran-Armitage Trend Test; P-value		NT	1.0000	0.0002*

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
liver				
dilatation, cystic, bile ducts				
Overall Rates (a)	2/70 (2.86%)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4964	0.4964	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.0573
dilatation, sinusoidal				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547
fibrosis				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	2/70 (2.86%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6530
focus of cellular alteration, basophilic				
Overall Rates (a)	30/70 (42.86%)	26/70 (37.14%)	32/70 (45.71%)	19/70 (27.14%)
Fisher's Exact Test; P-value		0.6050	0.8650	0.0759
Cochran-Armitage Trend Test; P-value		NT	NT	0.1382

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
liver				
focus of cellular alteration, clear				
Overall Rates (a)	2/70 (2.86%)	1/70 (1.43%)	3/70 (4.29%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.7488
focus of cellular alteration, eosinophilic				
Overall Rates (a)	10/70 (14.29%)	6/70 (8.57%)	12/70 (17.14%)	12/70 (17.14%)
Fisher's Exact Test; P-value		0.4264	0.8169	0.8169
Cochran-Armitage Trend Test; P-value		NT	NT	0.3603
hematopoiesis, extramedullary				
Overall Rates (a)	13/70 (18.57%)	26/70 (37.14%)	24/70 (34.29%)	11/70 (15.71%)
Fisher's Exact Test; P-value		0.0230	0.0545	0.8230
Cochran-Armitage Trend Test; P-value		NT	NT	0.6284
hyperplasia, bile duct				
Overall Rates (a)	34/70 (48.57%)	34/70 (48.57%)	34/70 (48.57%)	28/70 (40.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.3950
Cochran-Armitage Trend Test; P-value		NT	NT	0.3356

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
liver				
hypertrophy, hepatocyte, centrilobular				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	3/70 (4.29%)	65/70 (92.86%)
Fisher's Exact Test; P-value		1.0000	0.2446	0.0000
Cochran-Armitage Trend Test; P-value		1.0000	0.0330*	0.0000*
hypertrophy, hepatocyte, panlobular				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	3/70 (4.29%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.2446
Cochran-Armitage Trend Test; P-value		NT	1.0000	0.0197*
infiltration, mononuclear cell				
Overall Rates (a)	18/70 (25.71%)	11/70 (15.71%)	9/70 (12.86%)	17/70 (24.29%)
Fisher's Exact Test; P-value		0.2104	0.0854	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.7371
infiltration/inflammation, mixed cell				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
liver				
inflammation, acute				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797
inflammation, chronic-active				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797
leukocytosis, sinusoidal				
Overall Rates (a)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5263
macrophages, pigmented				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4369

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
liver				
multinucleated, hepatocytes				
Overall Rates (a)	2/70 (2.86%)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4964	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.0697
necrosis				
Overall Rates (a)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547
necrosis, focal				
Overall Rates (a)	5/70 (7.14%)	4/70 (5.71%)	6/70 (8.57%)	8/70 (11.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.5619
Cochran-Armitage Trend Test; P-value		NT	NT	0.2852
necrosis, hepatocytes, centrilobular				
Overall Rates (a)	1/70 (1.43%)	1/70 (1.43%)	4/70 (5.71%)	7/70 (10.00%)
Fisher's Exact Test; P-value		1.0000	0.3659	0.0625
Cochran-Armitage Trend Test; P-value		NT	0.1289	0.0078*

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
liver				
necrosis, individual hepatocyte				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	3/70 (4.29%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.2446
Cochran-Armitage Trend Test; P-value		NT	1.0000	0.0197*
vacuolation, centrilobular				
Overall Rates (a)	3/70 (4.29%)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.6195	0.2446	0.2446
Cochran-Armitage Trend Test; P-value		NT	0.0642	0.0246*
vacuolation, diffuse				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797
vacuolation, focal				
Overall Rates (a)	1/70 (1.43%)	1/70 (1.43%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.7955

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
liver				
vacuolation, median cleft				
Overall Rates (a)	1/70 (1.43%)	1/70 (1.43%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.7955
vacuolation, periportal				
Overall Rates (a)	17/70 (24.29%)	23/70 (32.86%)	22/70 (31.43%)	2/70 (2.86%)
Fisher's Exact Test; P-value		0.3497	0.4510	0.0003
Cochran-Armitage Trend Test; P-value		NT	0.3554	0.0035*
lung				
adenocarcinoma, malignant, secondary				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4369
bacterial colonies				
Overall Rates (a)	2/70 (2.86%)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4964	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.1951

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
lung				
congestion, chronic passive				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547
fibrosis				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797
foreign material				
Overall Rates (a)	0/70 (0.00%)	2/70 (2.86%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4964	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5263
granuloma				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	1.0000

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
lung				
hemorrhage				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	1.0000
histiocytosis, alveolar				
Overall Rates (a)	22/70 (31.43%)	20/70 (28.57%)	21/70 (30.00%)	42/70 (60.00%)
Fisher's Exact Test; P-value		0.8538	1.0000	0.0012
Cochran-Armitage Trend Test; P-value		NT	0.8540	0.0008*
infiltration, lymphoid, perivascular				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797
inflammation, acute				
Overall Rates (a)	0/70 (0.00%)	3/70 (4.29%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.2446	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	1.0000

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
lung				
inflammation, subacute/chronic				
Overall Rates (a)	1/70 (1.43%)	3/70 (4.29%)	1/70 (1.43%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.6195	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.3138
leukocytosis, vascular				
Overall Rates (a)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547
macrophages, pigmented alveolar				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	1.0000
mucus increased				
Overall Rates (a)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
lymph node, axillary				
erythrocytosis/erythrophagocytosis, sinus				
Overall Rates (a)	1/23 (4.35%)	0/22 (0.00%)	0/18 (0.00%)	1/12 (8.33%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.7403
histiocytosis, sinus				
Overall Rates (a)	1/23 (4.35%)	1/22 (4.55%)	1/18 (5.56%)	0/12 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6746
hyperplasia, lymphocyte/plasmacyte, medulla				
Overall Rates (a)	1/23 (4.35%)	2/22 (9.09%)	1/18 (5.56%)	1/12 (8.33%)
Fisher's Exact Test; P-value		0.6078	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.7503
lymph node, iliac				
dilatation, sinus				
Overall Rates (a)	0/1 (0.00%)	0/4 (0.00%)	1/3 (33.33%)	0/7 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9467

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Diagnosis				
lymph node, iliac				
hyperplasia, lymphocyte/plasmacyte, medulla				
Overall Rates (a)	0/1 (0.00%)	1/4 (25.00%)	0/3 (0.00%)	0/7 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2850
lymph node, mandibular				
dilatation, sinus				
Overall Rates (a)	0/69 (0.00%)	1/51 (1.96%)	0/56 (0.00%)	1/69 (1.45%)
Fisher's Exact Test; P-value		0.4250	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5541
erythrocytosis/erythrophagocytosis, sinus				
Overall Rates (a)	16/69 (23.19%)	11/51 (21.57%)	14/56 (25.00%)	8/69 (11.59%)
Fisher's Exact Test; P-value		1.0000	0.8359	0.1147
Cochran-Armitage Trend Test; P-value		NT	NT	0.1351
hyperplasia, lymphocyte/plasmacyte, medulla				
Overall Rates (a)	1/69 (1.45%)	1/51 (1.96%)	0/56 (0.00%)	1/69 (1.45%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.7932

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
lymph node, mesenteric				
dilatation, sinus				
Overall Rates (a)	2/70 (2.86%)	0/48 (0.00%)	1/56 (1.79%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.5133	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.2112
erythrocytosis/erythrophagocytosis, sinus				
Overall Rates (a)	1/70 (1.43%)	0/48 (0.00%)	1/56 (1.79%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5359
hyperplasia, lymphocyte/plasmacyte, medulla				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/56 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2094
mammary gland				
abscess				
Overall Rates (a)	1/70 (1.43%)	0/67 (0.00%)	0/66 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1847

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
mammary gland				
dilatation, gland/lumen				
Overall Rates (a)	1/70 (1.43%)	0/67 (0.00%)	0/66 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1847
galactoceles				
Overall Rates (a)	0/70 (0.00%)	3/67 (4.48%)	1/66 (1.52%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.1143	0.4853	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6586
hyperplasia, lobular				
Overall Rates (a)	64/70 (91.43%)	47/67 (70.15%)	56/66 (84.85%)	62/70 (88.57%)
Fisher's Exact Test; P-value		0.0020	0.2913	0.7792
Cochran-Armitage Trend Test; P-value		NT	NT	0.7801
nerve, sciatic				
degeneration, axonal/myelin				
Overall Rates (a)	37/70 (52.86%)	21/48 (43.75%)	23/55 (41.82%)	39/70 (55.71%)
Fisher's Exact Test; P-value		0.3544	0.2795	0.8654
Cochran-Armitage Trend Test; P-value		NT	NT	0.8060

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
nerve, sciatic				
inflammation, subacute/chronic				
Overall Rates (a)	0/70 (0.00%)	1/48 (2.08%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4068	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6640
nose, level a				
exudate, nasal passage				
Overall Rates (a)	0/70 (0.00%)	5/48 (10.42%)	2/55 (3.64%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.0098	0.1916	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9721
foreign material				
Overall Rates (a)	1/70 (1.43%)	2/48 (4.17%)	1/55 (1.82%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.5657	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.3820
hyperostosis				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
nose, level a				
inflammation				
Overall Rates (a)	1/70 (1.43%)	0/48 (0.00%)	1/55 (1.82%)	3/70 (4.29%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.6195
Cochran-Armitage Trend Test; P-value		NT	NT	0.1917
inflammation, hair follicle/epidermis				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
nose, level b				
degeneration				
Overall Rates (a)	1/70 (1.43%)	0/48 (0.00%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2009
exudate, nasal passage				
Overall Rates (a)	2/70 (2.86%)	6/48 (12.50%)	1/55 (1.82%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.0610	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2594

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
nose, level b				
foreign material				
Overall Rates (a)	1/70 (1.43%)	5/48 (10.42%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.0401	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1545
hyperostosis				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
inflammation				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	1/55 (1.82%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	0.4400	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2382
metaplasia, squamous				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
nose, level b				
mucus increased				
Overall Rates (a)	0/70 (0.00%)	1/48 (2.08%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4068	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6640
nose, level c				
erosion/ulcer				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
exudate, nasal passage				
Overall Rates (a)	0/70 (0.00%)	3/48 (6.25%)	1/55 (1.82%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.0648	0.4400	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8705
foreign material				
Overall Rates (a)	2/70 (2.86%)	2/48 (4.17%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	0.5032	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.3273

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
nose, level c				
hyperostosis				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
inflammation				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
mucus increased				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	1/55 (1.82%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4400	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6817
nose, level d				
degeneration/necrosis, olfactory epithelium				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	1/55 (1.82%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4400	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6817

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
nose, level d				
erosion/ulcer				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
exudate, nasal passage				
Overall Rates (a)	0/70 (0.00%)	2/48 (4.17%)	1/55 (1.82%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.1634	0.4400	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6888
foreign material				
Overall Rates (a)	1/70 (1.43%)	2/48 (4.17%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.5657	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6532
hyperostosis				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Diagnosis				
nose, level d				
inflammation				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
mucus increased				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	1/55 (1.82%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4400	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6817
ovaries				
cyst				
Overall Rates (a)	16/70 (22.86%)	16/50 (32.00%)	11/56 (19.64%)	13/70 (18.57%)
Fisher's Exact Test; P-value		0.2991	0.8274	0.6771
Cochran-Armitage Trend Test; P-value		NT	NT	0.3224
fibrosis				
Overall Rates (a)	0/70 (0.00%)	0/50 (0.00%)	0/56 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2067

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
ovaries				
hyperplasia, sex-cord/stromal				
Overall Rates (a)	9/70 (12.86%)	1/50 (2.00%)	4/56 (7.14%)	3/70 (4.29%)
Fisher's Exact Test; P-value		0.0442	0.3827	0.1284
Cochran-Armitage Trend Test; P-value		NT	NT	0.1008
pancreas				
atrophy, acinar				
Overall Rates (a)	9/70 (12.86%)	16/70 (22.86%)	10/70 (14.29%)	7/70 (10.00%)
Fisher's Exact Test; P-value		0.1848	1.0000	0.7914
Cochran-Armitage Trend Test; P-value		NT	NT	0.3699
bacterial colonies				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797
dilatation, duct				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
pancreas				
fibrosis				
Overall Rates (a)	4/70 (5.71%)	0/70 (0.00%)	2/70 (2.86%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.1196	0.6806	0.3659
Cochran-Armitage Trend Test; P-value		NT	NT	0.2316
hyperplasia, acinar cell, focal				
Overall Rates (a)	0/70 (0.00%)	2/70 (2.86%)	5/70 (7.14%)	5/70 (7.14%)
Fisher's Exact Test; P-value		0.4964	0.0581	0.0581
Cochran-Armitage Trend Test; P-value		0.1558	0.0188*	0.0177*
hyperplasia, islet cell				
Overall Rates (a)	1/70 (1.43%)	2/70 (2.86%)	1/70 (1.43%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.3685
polyarteritis				
Overall Rates (a)	2/70 (2.86%)	0/70 (0.00%)	2/70 (2.86%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.4964	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.8403

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
parathyroid glands				
hyperplasia, focal				
Overall Rates (a)	3/53 (5.66%)	1/37 (2.70%)	1/41 (2.44%)	1/53 (1.89%)
Fisher's Exact Test; P-value		0.6408	0.6295	0.6178
Cochran-Armitage Trend Test; P-value		NT	NT	0.2839
pituitary gland				
cyst				
Overall Rates (a)	1/70 (1.43%)	0/65 (0.00%)	0/65 (0.00%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4435
hyperplasia, diffuse, pars distalis				
Overall Rates (a)	3/70 (4.29%)	1/65 (1.54%)	1/65 (1.54%)	3/70 (4.29%)
Fisher's Exact Test; P-value		0.6204	0.6204	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	1.0000
hyperplasia, focal, pars distalis				
Overall Rates (a)	2/70 (2.86%)	0/65 (0.00%)	0/65 (0.00%)	4/70 (5.71%)
Fisher's Exact Test; P-value		0.4970	0.4970	0.6806
Cochran-Armitage Trend Test; P-value		NT	NT	0.2758

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
salivary gland, mandibular				
atrophy				
Overall Rates (a)	1/69 (1.45%)	0/47 (0.00%)	0/54 (0.00%)	0/69 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2012
salivary gland, parotid				
atrophy				
Overall Rates (a)	0/69 (0.00%)	1/48 (2.08%)	0/54 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4103	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6615
edema				
Overall Rates (a)	0/69 (0.00%)	0/48 (0.00%)	0/54 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2111
skeletal muscle, biceps femoris				
degeneration/necrosis, myofiber				
Overall Rates (a)	15/70 (21.43%)	0/48 (0.00%)	4/55 (7.27%)	14/70 (20.00%)
Fisher's Exact Test; P-value		0.0003	0.0429	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9969

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
skeletal muscle, biceps femoris				
degeneration/regeneration, myofiber				
Overall Rates (a)	0/70 (0.00%)	1/48 (2.08%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.4068	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5611
skin/skin, subcutis				
abscess				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
alopecia/hypotrichosis				
Overall Rates (a)	1/70 (1.43%)	2/48 (4.17%)	5/55 (9.09%)	9/70 (12.86%)
Fisher's Exact Test; P-value		0.5657	0.0860	0.0173
Cochran-Armitage Trend Test; P-value		0.3553	0.0451*	0.0050*
cyst, keratin				
Overall Rates (a)	0/70 (0.00%)	1/48 (2.08%)	1/55 (1.82%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4068	0.4400	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9862

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
skin/skin, subcutis				
erosion/ulcer				
Overall Rates (a)	1/70 (1.43%)	0/48 (0.00%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2009
hyperplasia, epidermal				
Overall Rates (a)	0/70 (0.00%)	1/48 (2.08%)	1/55 (1.82%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4068	0.4400	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9862
small intestine, duodenum				
hypertrophy/hyperplasia, goblet cell				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
small intestine, ileum				
hypertrophy/hyperplasia, goblet cell				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
small intestine, jejunum				
hypertrophy/hyperplasia, goblet cell				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
spinal cord, thoracic				
degeneration, axonal/myelin				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
spleen				
depletion, lymphoid, generalized				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/57 (0.00%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.0752
fibrosis, capsular				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	1/57 (1.75%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.4488	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6832

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
spleen				
hematopoiesis, extramedullary, increased				
Overall Rates (a)	31/70 (44.29%)	20/48 (41.67%)	25/57 (43.86%)	40/70 (57.14%)
Fisher's Exact Test; P-value		0.8509	1.0000	0.1761
Cochran-Armitage Trend Test; P-value		NT	NT	0.1334
stomach, glandular				
erosion/ulcer				
Overall Rates (a)	2/70 (2.86%)	0/48 (0.00%)	0/55 (0.00%)	3/70 (4.29%)
Fisher's Exact Test; P-value		0.5133	0.5032	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5865
fibrosis				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.0754
inflammation				
Overall Rates (a)	1/70 (1.43%)	0/48 (0.00%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2009

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
stomach, glandular				
mineralization				
Overall Rates (a)	0/70 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2096
stomach, nonglandular				
cyst, keratin				
Overall Rates (a)	1/70 (1.43%)	1/70 (1.43%)	0/70 (0.00%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6530
edema				
Overall Rates (a)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547
erosion/ulcer				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	2/70 (2.86%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.7955

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
stomach, nonglandular				
erosion/ulcer, limiting ridge				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.4964
Cochran-Armitage Trend Test; P-value		NT	NT	0.0697
hyperplasia, epithelial, limiting ridge				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	9/70 (12.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.0030
Cochran-Armitage Trend Test; P-value		NT	1.0000	0.0000*
hyperplasia, epithelial, nonglandular				
Overall Rates (a)	3/70 (4.29%)	3/70 (4.29%)	5/70 (7.14%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	0.7184	0.2446
Cochran-Armitage Trend Test; P-value		NT	NT	0.3364
inflammation				
Overall Rates (a)	4/70 (5.71%)	2/70 (2.86%)	6/70 (8.57%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.6806	0.7447	0.1196
Cochran-Armitage Trend Test; P-value		NT	NT	0.2920

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
thymus				
depletion, lymphoid, generalized				
Overall Rates (a)	67/68 (98.53%)	46/48 (95.83%)	51/55 (92.73%)	66/67 (98.51%)
Fisher's Exact Test; P-value		0.5686	0.1717	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.7760
hyperplasia, epithelial cell				
Overall Rates (a)	26/68 (38.24%)	21/48 (43.75%)	19/55 (34.55%)	21/67 (31.34%)
Fisher's Exact Test; P-value		0.5702	0.7098	0.4710
Cochran-Armitage Trend Test; P-value		NT	NT	0.2920
hyperplasia, lymphoid, medulla				
Overall Rates (a)	1/68 (1.47%)	3/48 (6.25%)	0/55 (0.00%)	2/67 (2.99%)
Fisher's Exact Test; P-value		0.3052	1.0000	0.6194
Cochran-Armitage Trend Test; P-value		NT	NT	0.9859
thyroid gland				
cyst, follicular				
Overall Rates (a)	0/69 (0.00%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2109

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
thyroid gland				
hyperplasia, c-cell, focal				
Overall Rates (a)	10/69 (14.49%)	3/48 (6.25%)	6/55 (10.91%)	7/70 (10.00%)
Fisher's Exact Test; P-value		0.2341	0.6010	0.4496
Cochran-Armitage Trend Test; P-value		NT	NT	0.5355
hyperplasia, follicular cell				
Overall Rates (a)	1/69 (1.45%)	0/48 (0.00%)	0/55 (0.00%)	2/70 (2.86%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4808
tongue				
erosion/ulcer				
Overall Rates (a)	0/70 (0.00%)	1/70 (1.43%)	1/70 (1.43%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.4369
hyperplasia, squamous cell				
Overall Rates (a)	2/70 (2.86%)	8/70 (11.43%)	4/70 (5.71%)	13/70 (18.57%)
Fisher's Exact Test; P-value		0.0967	0.6806	0.0047
Cochran-Armitage Trend Test; P-value		NT	0.4990	0.0088*

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Diagnosis				
tongue				
inflammation, acute				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797
inflammation, subacute/chronic				
Overall Rates (a)	3/70 (4.29%)	8/70 (11.43%)	4/70 (5.71%)	13/70 (18.57%)
Fisher's Exact Test; P-value		0.2076	1.0000	0.0146
Cochran-Armitage Trend Test; P-value		NT	0.7434	0.0208*
trachea				
inflammation, acute				
Overall Rates (a)	0/70 (0.00%)	1/48 (2.08%)	1/55 (1.82%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4068	0.4400	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9862
ureters				
dilatation				
Overall Rates (a)	4/70 (5.71%)	2/47 (4.26%)	0/54 (0.00%)	2/69 (2.90%)
Fisher's Exact Test; P-value		1.0000	0.1314	0.6806
Cochran-Armitage Trend Test; P-value		NT	NT	0.2188

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Diagnosis				
urinary bladder				
dilatation				
Overall Rates (a)	0/69 (0.00%)	1/48 (2.08%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4103	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6597
hemorrhage				
Overall Rates (a)	0/69 (0.00%)	1/48 (2.08%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4103	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6597
hyperplasia, simple transitional cell				
Overall Rates (a)	1/69 (1.45%)	1/48 (2.08%)	0/55 (0.00%)	3/70 (4.29%)
Fisher's Exact Test; P-value		1.0000	1.0000	0.6195
Cochran-Armitage Trend Test; P-value		NT	NT	0.3607
inflammation				
Overall Rates (a)	1/69 (1.45%)	1/48 (2.08%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.7829

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
urinary bladder				
leiomyosarcoma, malignant, secondary				
Overall Rates (a)	0/69 (0.00%)	1/48 (2.08%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		0.4103	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6597
uterus with cervix				
dilatation, gland/lumen				
Overall Rates (a)	17/70 (24.29%)	19/70 (27.14%)	22/70 (31.43%)	13/70 (18.57%)
Fisher's Exact Test; P-value		0.8469	0.4510	0.5371
Cochran-Armitage Trend Test; P-value		NT	NT	0.5810
hyperkeratosis				
Overall Rates (a)	2/70 (2.86%)	1/70 (1.43%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	0.4964	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.3685
hyperplasia, cervical fibromuscular				
Overall Rates (a)	1/70 (1.43%)	4/70 (5.71%)	1/70 (1.43%)	2/70 (2.86%)
Fisher's Exact Test; P-value		0.3659	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	1.0000

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
uterus with cervix				
hyperplasia, cystic endometrial				
Overall Rates (a)	1/70 (1.43%)	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.1797
hyperplasia, endometrial				
Overall Rates (a)	3/70 (4.29%)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		0.2446	0.2446	0.6195
Cochran-Armitage Trend Test; P-value		NT	NT	0.1774
hyperplasia, squamous cell				
Overall Rates (a)	4/70 (5.71%)	3/70 (4.29%)	1/70 (1.43%)	4/70 (5.71%)
Fisher's Exact Test; P-value		1.0000	0.3659	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.7922
metaplasia, squamous				
Overall Rates (a)	2/70 (2.86%)	0/70 (0.00%)	4/70 (5.71%)	2/70 (2.86%)
Fisher's Exact Test; P-value		0.4964	0.6806	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.5218

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Non-Neoplastic Lesions - FEMALE

Tissue Diagnosis	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
uterus with cervix				
thrombus				
Overall Rates (a)	0/70 (0.00%)	0/70 (0.00%)	1/70 (1.43%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.6547
vagina				
hyperplasia, fibromuscular				
Overall Rates (a)	1/70 (1.43%)	0/48 (0.00%)	0/55 (0.00%)	1/70 (1.43%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.9862
prolapse				
Overall Rates (a)	1/70 (1.43%)	0/48 (0.00%)	0/55 (0.00%)	0/70 (0.00%)
Fisher's Exact Test; P-value		1.0000	1.0000	1.0000
Cochran-Armitage Trend Test; P-value		NT	NT	0.2009

(a) - Number of animals with lesion/number of animals with the tissue examined

NT - Not Tested

Table 9
Individual Animal Final Body and Organ Weights

Codes For Individual Organ Weight Values

Abbreviations

BrWt – Brain Weight

BWt – Body Weight

gl – gland

w/ – with

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Interim

Group, Animal Number	Body weight g	Brain g	Brain/BWt %	Adrenal gl g	Adrenal gl/ BWt %	Adrenal gl/ BrWt ratio	Epididymides g	Epididymides/ BWt %	Epididymides/ BrWt ratio
<u>0 mg/kg/day</u>									
1001	630	2.251	0.3573	0.073	0.0116	0.0324	1.666	0.2644	0.7401
1002	838	2.437	0.2908	0.059	0.0070	0.0242	1.754	0.2093	0.7197
1003	796	2.338	0.2937	0.048	0.0060	0.0205	1.416	0.1779	0.6056
1004	728	2.368	0.3253	0.057	0.0078	0.0241	1.377	0.1891	0.5815
1005	963	2.153	0.2236	0.073	0.0076	0.0339	1.513	0.1571	0.7027
1006	1049	2.286	0.2179	0.057	0.0054	0.0249	1.679	0.1601	0.7345
1007	801	2.275	0.2840	0.049	0.0061	0.0215	1.297	0.1619	0.5701
1008	878	2.361	0.2689	0.084	0.0096	0.0356	1.395	0.1589	0.5909
1009	805	2.437	0.3027	0.053	0.0066	0.0217	1.518	0.1886	0.6229
1010	836	2.282	0.2730	0.056	0.0067	0.0245	1.532	0.1833	0.6713
<u>0.1 mg/kg/day</u>									
1081	718	2.529	0.3522	0.061	0.0085	0.0241	1.351	0.1882	0.5342
1082	1011	2.171	0.2147	0.082	0.0081	0.0378	1.461	0.1445	0.6730
1083	937	2.632	0.2809	0.087	0.0093	0.0331	1.297	0.1384	0.4928
1084	819	2.387	0.2915	0.062	0.0076	0.0260	1.354	0.1653	0.5672
1085	746	2.364	0.3169	0.049	0.0066	0.0207	1.384	0.1855	0.5854
1086	778	2.164	0.2781	0.060	0.0077	0.0277	1.510	0.1941	0.6978
1087	634	2.130	0.3360	0.049	0.0077	0.0230	1.418	0.2237	0.6657
1088	680	2.267	0.3334	0.095	0.0140	0.0419	1.446	0.2126	0.6378
1089	853	2.272	0.2664	0.073	0.0086	0.0321	1.376	0.1613	0.6056
1090	700	2.212	0.3160	0.071	0.0101	0.0321	1.547	0.2210	0.6994

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Interim

Group, Animal Number	Body weight g	Brain g	Brain/BWt %	Adrenal gl g	Adrenal gl/ BWt %	Adrenal gl/ BrWt ratio	Epididymides g	Epididymides/ BWt %	Epididymides/ BrWt ratio
<u>1 mg/kg/day</u>									
1161	810	2.357	0.2910	0.064	0.0079	0.0272	1.501	0.1853	0.6368
1162	785	2.200	0.2803	0.047	0.0060	0.0214	1.222	0.1557	0.5555
1163	850	2.082	0.2449	0.051	0.0060	0.0245	1.393	0.1639	0.6691
1164	697	2.011	0.2885	0.092	0.0132	0.0457	1.718	0.2465	0.8543
1165	715	2.359	0.3299	0.060	0.0084	0.0254	1.665	0.2329	0.7058
1166	866	2.184	0.2522	0.098	0.0113	0.0449	1.446	0.1670	0.6621
1167	761	2.221	0.2919	0.069	0.0091	0.0311	1.564	0.2055	0.7042
1168	794	2.366	0.2980	0.076	0.0096	0.0321	1.608	0.2025	0.6796
1169	791	2.344	0.2963	0.087	0.0110	0.0371	1.911	0.2416	0.8153
1170	725	2.288	0.3156	0.038	0.0052	0.0166	1.416	0.1953	0.6189
<u>50 mg/kg/day</u>									
1241	816	2.325	0.2849	0.092	0.0113	0.0396	1.703	0.2087	0.7325
1242	771	2.199	0.2852	0.035	0.0045	0.0159	1.360	0.1764	0.6185
1243	758	2.357	0.3109	0.060	0.0079	0.0255	1.265	0.1669	0.5367
1244	778	2.349	0.3019	0.082	0.0105	0.0349	1.491	0.1916	0.6347
1245	779	2.320	0.2978	0.055	0.0071	0.0237	1.287	0.1652	0.5547
1246	890	2.400	0.2697	0.110	0.0124	0.0458	1.626	0.1827	0.6775
1247	839	2.309	0.2752	0.073	0.0087	0.0316	1.684	0.2007	0.7293
1248	739	2.230	0.3018	0.057	0.0077	0.0256	1.496	0.2024	0.6709
1249 ^r	974	2.251	0.2311	0.104	0.0107	0.0462	1.650	0.1694	0.7330
1250	687	2.611	0.3801	0.076	0.0111	0.0291	1.568	0.2282	0.6005

^r Replacement animal

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Interim

Group, Animal Number	Heart	Heart/BWt	Heart/BrWt	Kidneys	Kidneys/BWt	Kidneys/BrWt	Liver	Liver/BWt	Liver/BrWt
	g	%	ratio	g	%	ratio	g	%	ratio
<u>0 mg/kg/day</u>									
1001	2.142	0.3400	0.9516	4.621	0.7335	2.0529	19.489	3.0935	8.6579
1002	2.215	0.2643	0.9089	6.107	0.7288	2.5059	28.193	3.3643	11.5687
1003	2.223	0.2793	0.9508	7.367	0.9255	3.1510	30.063	3.7768	12.8584
1004	2.046	0.2810	0.8640	5.321	0.7309	2.2470	19.352	2.6582	8.1723
1005	2.324	0.2413	1.0794	6.294	0.6536	2.9234	31.679	3.2896	14.7139
1006	2.475	0.2359	1.0827	6.853	0.6533	2.9978	34.746	3.3123	15.1995
1007	1.951	0.2436	0.8576	5.057	0.6313	2.2229	26.836	3.3503	11.7960
1008	2.210	0.2517	0.9360	5.556	0.6328	2.3532	27.313	3.1108	11.5684
1009	2.274	0.2825	0.9331	5.433	0.6749	2.2294	23.663	2.9395	9.7099
1010	2.387	0.2855	1.0460	5.578	0.6672	2.4443	27.860	3.3325	12.2086
<u>0.1 mg/kg/day</u>									
1081	2.029	0.2826	0.8023	5.542	0.7719	2.1914	27.846	3.8783	11.0107
1082	2.473	0.2446	1.1391	6.130	0.6063	2.8236	33.461	3.3097	15.4127
1083	2.361	0.2520	0.8970	6.423	0.6855	2.4403	31.236	3.3336	11.8678
1084	2.087	0.2548	0.8743	4.892	0.5973	2.0494	26.530	3.2393	11.1144
1085	2.087	0.2798	0.8828	5.633	0.7551	2.3828	24.947	3.3441	10.5529
1086	1.979	0.2544	0.9145	5.098	0.6553	2.3558	23.091	2.9680	10.6705
1087	1.757	0.2771	0.8249	4.473	0.7055	2.1000	18.735	2.9550	8.7958
1088	1.991	0.2928	0.8783	4.944	0.7271	2.1809	23.657	3.4790	10.4354
1089	2.017	0.2365	0.8878	4.741	0.5558	2.0867	28.178	3.3034	12.4023
1090	2.087	0.2981	0.9435	5.619	0.8027	2.5402	23.543	3.3633	10.6433

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Interim

Group, Animal Number	Heart	Heart/BWt	Heart/BrWt	Kidneys	Kidneys/BWt	Kidneys/BrWt	Liver	Liver/BWt	Liver/BrWt
	g	%	ratio	g	%	ratio	g	%	ratio
<u>1 mg/kg/day</u>									
1161	1.978	0.2442	0.8392	5.045	0.6228	2.1404	25.982	3.2077	11.0233
1162	2.092	0.2665	0.9509	5.118	0.6520	2.3264	26.405	3.3637	12.0023
1163	2.180	0.2565	1.0471	5.348	0.6292	2.5687	24.905	2.9300	11.9621
1164	2.147	0.3080	1.0676	5.083	0.7293	2.5276	23.003	3.3003	11.4386
1165	2.080	0.2909	0.8817	5.456	0.7631	2.3128	25.753	3.6018	10.9169
1166	2.120	0.2448	0.9707	5.177	0.5978	2.3704	29.397	3.3946	13.4602
1167	2.210	0.2904	0.9950	5.121	0.6729	2.3057	23.339	3.0669	10.5083
1168	2.458	0.3096	1.0389	6.177	0.7780	2.6107	26.854	3.3821	11.3500
1169	2.848	0.3601	1.2150	5.394	0.6819	2.3012	25.866	3.2700	11.0350
1170	1.900	0.2621	0.8304	4.148	0.5721	1.8129	23.719	3.2716	10.3667
<u>50 mg/kg/day</u>									
1241	2.142	0.2625	0.9213	6.015	0.7371	2.5871	29.313	3.5923	12.6077
1242	2.263	0.2935	1.0291	5.048	0.6547	2.2956	24.889	3.2281	11.3183
1243	1.859	0.2453	0.7887	4.917	0.6487	2.0861	23.772	3.1361	10.0857
1244	2.183	0.2806	0.9293	5.272	0.6776	2.2444	28.604	3.6766	12.1771
1245	2.016	0.2588	0.8690	5.450	0.6996	2.3491	26.162	3.3584	11.2767
1246	2.312	0.2598	0.9633	6.580	0.7393	2.7417	37.455	4.2084	15.6063
1247	2.479	0.2955	1.0736	6.943	0.8275	3.0069	36.535	4.3546	15.8229
1248	2.125	0.2876	0.9529	5.245	0.7097	2.3520	28.573	3.8664	12.8130
1249 ^r	2.410	0.2474	1.0706	6.768	0.6949	3.0067	35.510	3.6458	15.7752
1250	1.981	0.2884	0.7587	5.367	0.7812	2.0555	26.419	3.8456	10.1183

^r Replacement animal

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Interim

Group, Animal Number	Spleen g	Spleen/BWt %	Spleen/BrWt ratio	Testes g	Testes/BWt %	Testes/BrWt ratio	Thyroid/ parathyroid gl g	Thyroid/ parathyroid gl/ BWt %	Thyroid/ parathyroid gl/ BrWt ratio
<u>0 mg/kg/day</u>									
1001	1.117	0.1773	0.4962	3.794	0.6022	1.6855	0.043	0.0069	0.0192
1002	1.281	0.1529	0.5256	4.201	0.5013	1.7238	0.037	0.0044	0.0152
1003	1.209	0.1519	0.5171	4.212	0.5291	1.8015	0.034	0.0042	0.0145
1004	1.064	0.1462	0.4493	3.296	0.4527	1.3919	0.031	0.0042	0.0129
1005	1.363	0.1415	0.6331	3.555	0.3692	1.6512	0.046	0.0048	0.0215
1006	1.384	0.1319	0.6054	3.506	0.3342	1.5337	0.040	0.0038	0.0176
1007	1.179	0.1472	0.5182	3.206	0.4002	1.4092	0.039	0.0048	0.0170
1008	1.180	0.1344	0.4998	3.620	0.4123	1.5332	0.045	0.0051	0.0188
1009	1.283	0.1594	0.5265	3.464	0.4303	1.4214	0.038	0.0047	0.0154
1010	1.302	0.1557	0.5706	4.012	0.4799	1.7581	0.048	0.0057	0.0208
<u>0.1 mg/kg/day</u>									
1081	1.067	0.1486	0.4219	3.681	0.5127	1.4555	0.039	0.0054	0.0154
1082	1.195	0.1182	0.5504	4.091	0.4046	1.8844	0.036	0.0036	0.0168
1083	1.273	0.1359	0.4837	3.542	0.3780	1.3457	0.045	0.0048	0.0172
1084	1.052	0.1284	0.4407	3.979	0.4858	1.6669	0.056	0.0068	0.0235
1085	0.996	0.1335	0.4213	4.199	0.5629	1.7762	0.053	0.0071	0.0223
1086	1.214	0.1560	0.5610	4.259	0.5474	1.9681	0.043	0.0055	0.0198
1087	0.902	0.1423	0.4235	3.799	0.5992	1.7836	0.042	0.0066	0.0198
1088	0.919	0.1351	0.4054	4.343	0.6387	1.9157	0.032	0.0047	0.0142
1089	0.902	0.1057	0.3970	3.797	0.4451	1.6712	0.045	0.0053	0.0199
1090	1.167	0.1667	0.5276	3.960	0.5657	1.7902	0.029	0.0041	0.0130

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Interim

Group, Animal Number	Spleen g	Spleen/BWt %	Spleen/BrWt ratio	Testes g	Testes/BWt %	Testes/BrWt ratio	Thyroid/ parathyroid gl g	Thyroid/ parathyroid gl/ BWt %	Thyroid/ parathyroid gl/ BrWt ratio
<u>1 mg/kg/day</u>									
1161	1.084	0.1338	0.4599	4.077	0.5033	1.7297	0.044	0.0055	0.0188
1162	0.963	0.1227	0.4377	3.487	0.4442	1.5850	0.046	0.0058	0.0208
1163	1.246	0.1466	0.5985	2.881	0.3389	1.3838	0.029	0.0034	0.0137
1164	1.163	0.1669	0.5783	4.290	0.6155	2.1333	0.033	0.0048	0.0165
1165	1.017	0.1422	0.4311	4.648	0.6501	1.9703	0.041	0.0057	0.0173
1166	1.104	0.1275	0.5055	3.904	0.4508	1.7875	0.046	0.0053	0.0211
1167	1.372	0.1803	0.6177	4.616	0.6066	2.0783	0.046	0.0061	0.0208
1168	1.255	0.1581	0.5304	3.933	0.4953	1.6623	0.104	0.0131	0.0439
1169	1.108	0.1401	0.4727	4.711	0.5956	2.0098	0.046	0.0059	0.0198
1170	0.944	0.1302	0.4126	4.020	0.5545	1.7570	0.045	0.0062	0.0195
<u>50 mg/kg/day</u>									
1241	1.037	0.1271	0.4460	3.817	0.4678	1.6417	0.044	0.0054	0.0189
1242	0.982	0.1274	0.4466	4.034	0.5232	1.8345	0.035	0.0045	0.0159
1243	1.146	0.1512	0.4862	3.868	0.5103	1.6411	0.038	0.0050	0.0161
1244	0.994	0.1278	0.4232	4.222	0.5427	1.7974	0.043	0.0055	0.0182
1245	1.260	0.1617	0.5431	3.063	0.3932	1.3203	0.035	0.0045	0.0152
1246	1.421	0.1597	0.5921	5.751	0.6462	2.3963	0.054	0.0060	0.0223
1247	1.577	0.1880	0.6830	4.112	0.4901	1.7809	0.044	0.0052	0.0189
1248	1.021	0.1382	0.4578	4.156	0.5624	1.8637	0.040	0.0054	0.0178
1249 ^r	1.574	0.1616	0.6992	4.431	0.4549	1.9685	0.050	0.0051	0.0221
1250	1.206	0.1755	0.4619	4.678	0.6809	1.7917	0.033	0.0047	0.0125

^r Replacement animal

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Interim

Group, Animal Number	Body weight g	Brain g	Brain/BWt %	Adrenal gl g	Adrenal gl/ BWt %	Adrenal gl/ BrWt ratio	Heart g	Heart/BWt %	Heart/BrWt ratio
<u>0 mg/kg/day</u>									
1322	393	1.796	0.4570	0.087	0.0221	0.0484	1.338	0.3405	0.7450
1324	432	2.015	0.4664	0.064	0.0148	0.0318	1.283	0.2970	0.6367
1325	364	1.798	0.4940	0.054	0.0148	0.0300	1.156	0.3176	0.6429
1326	425	2.013	0.4736	0.053	0.0125	0.0263	1.321	0.3108	0.6562
1327	448	2.060	0.4598	0.083	0.0185	0.0403	1.330	0.2969	0.6456
1328	408	2.032	0.4980	0.073	0.0179	0.0359	1.312	0.3216	0.6457
1329	419	2.046	0.4883	0.105	0.0251	0.0513	1.176	0.2807	0.5748
1330	598	1.833	0.3065	0.109	0.0182	0.0595	2.412	0.4033	1.3159
1331	495	2.072	0.4186	0.062	0.0125	0.0299	1.591	0.3214	0.7679
1332	532	2.019	0.3795	0.096	0.0180	0.0475	1.474	0.2771	0.7301
<u>1 mg/kg/day</u>									
1401	346	1.997	0.5772	0.043	0.0124	0.0215	1.190	0.3439	0.5959
1402	375	1.915	0.5107	0.100	0.0267	0.0522	1.224	0.3264	0.6392
1403	350	2.034	0.5811	0.089	0.0254	0.0438	1.205	0.3443	0.5924
1404	362	2.004	0.5536	0.081	0.0224	0.0404	1.152	0.3182	0.5749
1405	333	1.807	0.5426	0.114	0.0342	0.0631	1.188	0.3568	0.6574
1406	459	2.038	0.4440	0.073	0.0159	0.0358	1.301	0.2834	0.6384
1407	465	2.022	0.4348	0.088	0.0189	0.0435	1.340	0.2882	0.6627
1408	473	2.033	0.4298	0.060	0.0127	0.0295	1.274	0.2693	0.6267
1409	405	1.937	0.4783	0.065	0.0160	0.0336	1.312	0.3240	0.6773
1410	481	2.016	0.4191	0.055	0.0114	0.0273	1.342	0.2790	0.6657

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Interim

Group, Animal Number	Body weight g	Brain g	Brain/BWt %	Adrenal gl g	Adrenal gl/ BWt %	Adrenal gl/ BrWt ratio	Heart g	Heart/BWt %	Heart/BrWt ratio
<u>50 mg/kg/day</u>									
1481	408	1.960	0.4804	0.094	0.0230	0.0480	1.195	0.2929	0.6097
1482	568	1.947	0.3428	0.106	0.0187	0.0544	1.620	0.2852	0.8320
1483	429	1.971	0.4594	0.106	0.0247	0.0538	1.284	0.2993	0.6514
1484	479	2.160	0.4509	0.088	0.0184	0.0407	1.389	0.2900	0.6431
1485	347	2.087	0.6014	0.064	0.0184	0.0307	1.032	0.2974	0.4945
1486	565	2.014	0.3565	0.114	0.0202	0.0566	1.514	0.2680	0.7517
1487	457	1.984	0.4341	0.071	0.0155	0.0358	1.310	0.2867	0.6603
1488	296	2.006	0.6777	0.102	0.0345	0.0508	1.127	0.3807	0.5618
1489	412	1.916	0.4650	0.074	0.0180	0.0386	1.131	0.2745	0.5903
1490	490	1.915	0.3908	0.091	0.0186	0.0475	1.642	0.3351	0.8574
<u>500 mg/kg/day</u>									
1561	342	1.936	0.5661	0.088	0.0257	0.0455	1.185	0.3465	0.6121
1562	270	2.000	0.7407	0.054	0.0200	0.0270	0.926	0.3430	0.4630
1563	397	1.824	0.4594	0.304	0.0766	0.1667	1.195	0.3010	0.6552
1564	321	1.842	0.5738	0.069	0.0215	0.0375	1.132	0.3526	0.6145
1565	325	1.915	0.5892	0.072	0.0222	0.0376	1.257	0.3868	0.6564
1568	408	1.949	0.4777	0.103	0.0252	0.0528	1.299	0.3184	0.6665
1569	444	2.025	0.4561	0.085	0.0191	0.0420	1.432	0.3225	0.7072
1570	350	1.928	0.5509	0.078	0.0223	0.0405	1.353	0.3866	0.7018
1571	407	1.904	0.4678	0.052	0.0128	0.0273	1.173	0.2882	0.6161
1572	363	1.975	0.5441	0.071	0.0196	0.0359	1.271	0.3501	0.6435

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Interim

Group, Animal Number	Kidneys g	Kidneys/BWt %	Kidneys/BrWt ratio	Liver g	Liver/BWt %	Liver/BrWt ratio	Ovaries w/ oviducts g	Ovaries w/ oviducts/BWt %	Ovaries w/ oviducts/BrWt ratio
<u>0 mg/kg/day</u>									
1322	2.434	0.6193	1.3552	11.439	2.9107	6.3692	0.090	0.0229	0.0501
1324	2.731	0.6322	1.3553	12.089	2.7984	5.9995	0.117	0.0271	0.0581
1325	2.304	0.6330	1.2814	11.603	3.1876	6.4533	0.084	0.0231	0.0467
1326	2.735	0.6435	1.3587	11.442	2.6922	5.6841	0.116	0.0273	0.0576
1327	2.781	0.6208	1.3500	12.060	2.6920	5.8544	0.101	0.0225	0.0490
1328	2.590	0.6348	1.2746	12.883	3.1576	6.3401	0.089	0.0218	0.0438
1329	2.816	0.6721	1.3763	12.939	3.0881	6.3240	0.111	0.0265	0.0543
1330	4.193	0.7012	2.2875	19.849	3.3192	10.8287	0.121	0.0202	0.0660
1331	2.826	0.5709	1.3639	14.088	2.8461	6.7992	0.107	0.0216	0.0516
1332	3.086	0.5801	1.5285	13.605	2.5573	6.7385	0.112	0.0211	0.0555
<u>1 mg/kg/day</u>									
1401	2.351	0.6795	1.1773	11.128	3.2162	5.5724	0.199	0.0575	0.0996
1402	2.801	0.7469	1.4627	11.122	2.9659	5.8078	0.096	0.0256	0.0501
1403	2.719	0.7769	1.3368	10.505	3.0014	5.1647	0.070	0.0200	0.0344
1404	2.627	0.7257	1.3109	11.451	3.1633	5.7141	0.110	0.0304	0.0549
1405	2.721	0.8171	1.5058	11.435	3.4339	6.3282	0.137	0.0411	0.0758
1406	2.941	0.6407	1.4431	14.671	3.1963	7.1987	0.131	0.0285	0.0643
1407	2.685	0.5774	1.3279	11.980	2.5763	5.9248	0.077	0.0166	0.0381
1408	2.819	0.5960	1.3866	13.633	2.8822	6.7059	0.143	0.0302	0.0703
1409	2.409	0.5948	1.2437	9.847	2.4314	5.0836	0.167	0.0412	0.0862
1410	2.875	0.5977	1.4261	13.837	2.8767	6.8636	0.080	0.0166	0.0397

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Interim

Group, Animal Number	Kidneys	Kidneys/BWt	Kidneys/BrWt	Liver	Liver/BWt	Liver/BrWt	Ovaries w/ oviducts	Ovaries w/ oviducts/BWt	Ovaries w/ oviducts/BrWt
	g	%	ratio	g	%	ratio	g	%	ratio
<u>50 mg/kg/day</u>									
1481	3.239	0.7939	1.6526	15.393	3.7728	7.8536	0.076	0.0186	0.0388
1482	2.741	0.4826	1.4078	17.941	3.1586	9.2147	0.123	0.0217	0.0632
1483	2.929	0.6828	1.4860	11.986	2.7939	6.0812	0.154	0.0359	0.0781
1484	3.230	0.6743	1.4954	15.664	3.2701	7.2519	0.119	0.0248	0.0551
1485	2.594	0.7476	1.2429	10.450	3.0115	5.0072	0.163	0.0470	0.0781
1486	3.123	0.5527	1.5506	22.113	3.9138	10.9796	0.222	0.0393	0.1102
1487	2.679	0.5862	1.3503	13.063	2.8584	6.5842	0.087	0.0190	0.0439
1488	2.529	0.8544	1.2607	10.722	3.6223	5.3450	0.102	0.0345	0.0508
1489	2.930	0.7112	1.5292	13.688	3.3223	7.1441	0.134	0.0325	0.0699
1490	3.639	0.7427	1.9003	16.521	3.3716	8.6272	0.158	0.0322	0.0825
<u>500 mg/kg/day</u>									
1561	3.088	0.9029	1.5950	17.492	5.1146	9.0351	0.093	0.0272	0.0480
1562	2.426	0.8985	1.2130	13.376	4.9541	6.6880	0.058	0.0215	0.0290
1563	2.898	0.7300	1.5888	18.345	4.6209	10.0576	0.070	0.0176	0.0384
1564	2.551	0.7947	1.3849	16.090	5.0125	8.7351	0.161	0.0502	0.0874
1565	2.861	0.8803	1.4940	16.134	4.9643	8.4251	0.121	0.0372	0.0632
1568	3.008	0.7373	1.5434	17.830	4.3701	9.1483	0.117	0.0287	0.0600
1569	2.800	0.6306	1.3827	22.186	4.9968	10.9560	0.254	0.0572	0.1254
1570	3.146	0.8989	1.6317	21.198	6.0566	10.9948	0.122	0.0349	0.0633
1571	2.522	0.6197	1.3246	15.876	3.9007	8.3382	0.081	0.0199	0.0425
1572	2.768	0.7625	1.4015	17.359	4.7821	8.7894	0.108	0.0298	0.0547

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Interim

Group, Animal Number	Spleen g	Spleen/BWt %	Spleen/BrWt ratio	Thyroid/ parathyroid gl g	Thyroid/ parathyroid gl/ BWt %	Thyroid/ parathyroid gl/ BrWt ratio	Uterus w/ cervix g	Uterus w/ cervix/BWt %	Uterus w/ cervix/BrWt ratio
<u>0 mg/kg/day</u>									
1322	0.621	0.1580	0.3458	0.022	0.0057	0.0125	1.061	0.2700	0.5908
1324	0.715	0.1655	0.3548	0.029	0.0067	0.0144	0.439	0.1016	0.2179
1325	0.590	0.1621	0.3281	0.024	0.0065	0.0131	0.922	0.2533	0.5128
1326	0.624	0.1468	0.3100	0.024	0.0057	0.0121	0.668	0.1572	0.3318
1327	0.727	0.1623	0.3529	0.024	0.0052	0.0114	1.093	0.2440	0.5306
1328	0.683	0.1674	0.3361	0.034	0.0084	0.0169	0.759	0.1860	0.3735
1329	0.680	0.1623	0.3324	0.021	0.0051	0.0104	1.225	0.2924	0.5987
1330	0.880	0.1472	0.4801	0.039	0.0065	0.0213	1.029	0.1721	0.5614
1331	0.643	0.1299	0.3103	0.028	0.0057	0.0137	0.998	0.2016	0.4817
1332	0.779	0.1464	0.3858	0.040	0.0075	0.0199	0.692	0.1301	0.3427
<u>1 mg/kg/day</u>									
1401	0.678	0.1960	0.3395	0.017	0.0049	0.0084	0.669	0.1934	0.3350
1402	0.664	0.1771	0.3467	0.024	0.0063	0.0123	1.118	0.2981	0.5838
1403	0.492	0.1406	0.2419	0.023	0.0066	0.0113	0.858	0.2451	0.4218
1404	0.583	0.1610	0.2909	0.025	0.0068	0.0123	0.930	0.2569	0.4641
1405	0.560	0.1682	0.3099	0.023	0.0068	0.0126	1.456	0.4372	0.8058
1406	0.649	0.1414	0.3184	0.027	0.0059	0.0134	0.626	0.1364	0.3072
1407	0.654	0.1406	0.3234	0.030	0.0065	0.0148	0.963	0.2071	0.4763
1408	0.622	0.1315	0.3060	0.031	0.0066	0.0153	0.712	0.1505	0.3502
1409	0.552	0.1363	0.2850	0.030	0.0075	0.0156	0.623	0.1538	0.3216
1410	0.677	0.1407	0.3358	0.024	0.0049	0.0117	1.140	0.2370	0.5655

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Interim

Group, Animal Number	Spleen g	Spleen/BWt %	Spleen/BrWt ratio	Thyroid/ parathyroid gl g	Thyroid/ parathyroid gl/ BWt %	Thyroid/ parathyroid gl/ BrWt ratio	Uterus w/ cervix g	Uterus w/ cervix/BWt %	Uterus w/ cervix/BrWt ratio
<u>50 mg/kg/day</u>									
1481	0.478	0.1172	0.2439	0.026	0.0064	0.0134	1.130	0.2770	0.5765
1482	0.769	0.1354	0.3950	0.054	0.0095	0.0278	1.281	0.2255	0.6579
1483	0.677	0.1578	0.3435	0.028	0.0065	0.0141	1.310	0.3054	0.6646
1484	0.586	0.1223	0.2713	0.029	0.0060	0.0133	1.326	0.2768	0.6139
1485	0.459	0.1323	0.2199	0.033	0.0096	0.0160	1.262	0.3637	0.6047
1486	0.752	0.1331	0.3734	0.043	0.0076	0.0213	1.390	0.2460	0.6902
1487	0.564	0.1234	0.2843	0.024	0.0053	0.0122	1.202	0.2630	0.6058
1488	0.720	0.2432	0.3589	0.022	0.0074	0.0109	0.962	0.3250	0.4796
1489	0.556	0.1350	0.2902	0.021	0.0050	0.0107	1.113	0.2701	0.5809
1490	0.580	0.1184	0.3029	0.032	0.0064	0.0164	0.739	0.1508	0.3859
<u>500 mg/kg/day</u>									
1561	0.530	0.1550	0.2738	0.024	0.0070	0.0124	1.170	0.3421	0.6043
1562	0.390	0.1444	0.1950	0.029	0.0107	0.0145	0.436	0.1615	0.2180
1563	0.540	0.1360	0.2961	0.036	0.0090	0.0197	1.029	0.2592	0.5641
1564	0.582	0.1813	0.3160	0.024	0.0075	0.0131	0.729	0.2271	0.3958
1565	0.520	0.1600	0.2715	0.025	0.0077	0.0130	1.839	0.5658	0.9603
1568	0.607	0.1488	0.3114	0.025	0.0062	0.0129	1.106	0.2711	0.5675
1569	0.626	0.1410	0.3091	0.043	0.0098	0.0214	0.439	0.0989	0.2168
1570	0.653	0.1866	0.3387	0.026	0.0073	0.0132	1.221	0.3489	0.6333
1571	0.552	0.1356	0.2899	0.029	0.0072	0.0154	0.949	0.2332	0.4984
1572	0.660	0.1818	0.3342	0.033	0.0090	0.0165	1.766	0.4865	0.8942

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Terminal

Group, Animal Number	Body weight g	Brain g	Brain/BWt %	Adrenal gl g	Adrenal gl/ BWt %	Adrenal gl/ BrWt ratio	Epididymides g	Epididymides/ BWt %	Epididymides/ BrWt ratio
<u>0 mg/kg/day</u>									
1011	811	2.358	0.2908	0.097	0.0120	0.0411	1.345	0.1658	0.5704
1014	851	2.367	0.2781	0.090	0.0106	0.0380	1.275	0.1498	0.5387
1015	897	2.306	0.2571	0.056	0.0062	0.0243	1.420	0.1583	0.6158
1025	985	2.334	0.2370	0.115	0.0117	0.0493	1.387	0.1408	0.5943
1026	656	2.070	0.3155	0.101	0.0154	0.0488	1.654	0.2521	0.7990
1029	960	2.796	0.2913	0.102	0.0106	0.0365	1.455	0.1516	0.5204
1031	685	2.411	0.3520	0.099	0.0145	0.0411	1.034	0.1509	0.4289
1035	932	2.351	0.2523	0.076	0.0082	0.0323	1.456	0.1562	0.6193
1036	595	1.986	0.3338	0.102	0.0171	0.0514	1.269	0.2133	0.6390
1041	893	2.510	0.2811	0.077	0.0086	0.0307	1.254	0.1404	0.4996
1045	852	2.392	0.2808	0.081	0.0095	0.0339	1.528	0.1793	0.6388
1062	863	2.237	0.2592	0.095	0.0110	0.0425	1.469	0.1702	0.6567
1067	808	2.336	0.2891	0.089	0.0110	0.0381	1.459	0.1806	0.6246
1068	788	2.370	0.3008	0.103	0.0131	0.0435	1.268	0.1609	0.5350
1076	873	2.266	0.2596	0.292 ^e	0.0334 ^e	0.1289 ^e	1.871	0.2143	0.8257
<u>0.1 mg/kg/day</u>									
1091	745	2.374	0.3187	0.077	0.0103	0.0324	1.506	0.2021	0.6344
1093	638	2.476	0.3881	0.126	0.0197	0.0509	1.240	0.1944	0.5008
1094	884	2.328	0.2633	0.070	0.0079	0.0301	1.414	0.1600	0.6074
1096	1045	2.339	0.2238	0.157	0.0150	0.0671	1.623	0.1553	0.6939
1097	976	2.286	0.2342	0.127	0.0130	0.0556	1.568	0.1607	0.6859
1099	859	2.433	0.2832	0.083 ^e	0.0097 ^e	0.0341 ^e	1.332	0.1551	0.5475

^e Excluded from the mean

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Terminal

Group, Animal Number	Body weight g	Brain g	Brain/BWt %	Adrenal gl g	Adrenal gl/ BWt %	Adrenal gl/ BrWt ratio	Epididymides g	Epididymides/ BWt %	Epididymides/ BrWt ratio
<u>0.1 mg/kg/day</u>									
1107	887	2.364	0.2665	0.055	0.0062	0.0233	1.260	0.1421	0.5330
1109	704	2.205	0.3132	0.046	0.0065	0.0209	1.314	0.1866	0.5959
1112	1056	2.196	0.2080	0.086	0.0081	0.0392	1.567	0.1484	0.7136
1120	853	2.406	0.2821	0.267 ^e	0.0313 ^e	0.1110 ^e	1.378	0.1615	0.5727
1122	821	2.478	0.3018	1.934 ^e	0.2356 ^e	0.7805 ^e	1.487	0.1811	0.6001
1123	1181	2.589	0.2192	0.113	0.0096	0.0436	1.546	0.1309	0.5971
1124	623	2.357	0.3783	0.070	0.0112	0.0297	1.249	0.2005	0.5299
1127	667	2.158	0.3235	0.118	0.0177	0.0547	1.317	0.1975	0.6103
1132	866	2.308	0.2665	0.080	0.0092	0.0347	1.358	0.1568	0.5884
1140	906	2.180	0.2406	0.105	0.0116	0.0482	1.578	0.1742	0.7239
1143	550	2.098	0.3815	0.093	0.0169	0.0443	0.960	0.1745	0.4576
1147	914	2.486	0.2720	0.091	0.0100	0.0366	1.500	0.1641	0.6034
1150	738	2.210	0.2995	0.063	0.0085	0.0285	1.257	0.1703	0.5688
1154	832	1.949	0.2343	0.115	0.0138	0.0590	1.378	0.1656	0.7070
<u>1 mg/kg/day</u>									
1171	664	2.339	0.3523	0.038	0.0057	0.0162	0.862	0.1298	0.3685
1176	786	2.306	0.2934	0.055	0.0070	0.0239	1.424	0.1812	0.6175
1178	660	2.213	0.3353	0.121	0.0183	0.0547	1.317	0.1995	0.5951
1180	863	2.283	0.2645	0.088	0.0102	0.0385	1.178	0.1365	0.5160
1186	643	2.377	0.3697	0.068	0.0106	0.0286	1.413	0.2198	0.5944
1192	855	2.275	0.2661	0.104	0.0122	0.0457	1.484	0.1736	0.6523
1193	723	2.355	0.3257	0.093	0.0129	0.0395	1.325	0.1833	0.5626

^e Excluded from the mean

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Terminal

Group, Animal Number	Body weight g	Brain g	Brain/BWt %	Adrenal gl g	Adrenal gl/ BWt %	Adrenal gl/ BrWt ratio	Epididymides g	Epididymides/ BWt %	Epididymides/ BrWt ratio
<u>1 mg/kg/day</u>									
1194	453	2.299	0.5075	0.044	0.0097	0.0191	0.964	0.2128	0.4193
1199	747	2.184	0.2924	0.102	0.0137	0.0467	1.834	0.2455	0.8397
1204	773	2.221	0.2873	0.088	0.0114	0.0396	1.295	0.1675	0.5831
1211	987	2.409	0.2441	0.142	0.0144	0.0589	1.360	0.1378	0.5645
1212	671	2.154	0.3210	0.078	0.0116	0.0362	1.518	0.2262	0.7047
1218	877	2.499	0.2849	0.133	0.0152	0.0532	1.336	0.1523	0.5346
1221	725	2.290	0.3159	0.085	0.0117	0.0371	1.319	0.1819	0.5760
1223	902	2.288	0.2537	0.065	0.0072	0.0284	1.238	0.1373	0.5411
1225	959	2.440	0.2544	0.088	0.0092	0.0361	1.734	0.1808	0.7107
1227	655	2.311	0.3528	0.084	0.0128	0.0363	1.461	0.2231	0.6322
1240	790	2.187	0.2768	0.071	0.0090	0.0325	1.105	0.1399	0.5053
<u>50 mg/kg/day</u>									
1251	743	2.277	0.3065	0.080	0.0108	0.0351	1.262	0.1699	0.5542
1252	1033	2.370	0.2294	0.243 ^e	0.0235 ^e	0.1025 ^e	1.371	0.1327	0.5785
1254	702	2.194	0.3125	0.048	0.0068	0.0219	1.835	0.2614	0.8364
1257	879	2.435	0.2770	0.114	0.0130	0.0468	1.649	0.1876	0.6772
1261	791	2.485	0.3142	0.113	0.0143	0.0455	1.411	0.1784	0.5678
1270	879	2.347	0.2670	0.062	0.0071	0.0264	1.434	0.1631	0.6110
1277	914	2.292	0.2508	0.068	0.0074	0.0297	1.516	0.1659	0.6614
1283	748	2.326	0.3110	0.079	0.0106	0.0340	1.399	0.1870	0.6015
1286	906	2.323	0.2564	0.133	0.0147	0.0573	1.399	0.1544	0.6022
1287	861	2.476	0.2876	0.125	0.0145	0.0505	1.459	0.1695	0.5893

^e Excluded from the mean

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Terminal

Group, Animal Number	Body weight g	Brain g	Brain/BWt %	Adrenal gl g	Adrenal gl/ BWt %	Adrenal gl/ BrWt ratio	Epididymides g	Epididymides/ BWt %	Epididymides/ BrWt ratio
<u>50 mg/kg/day</u>									
1289	961	2.271	0.2363	0.750 ^e	0.0780 ^e	0.3303 ^e	1.266	0.1317	0.5575
1294	658	2.121	0.3223	0.053	0.0081	0.0250	1.451	0.2205	0.6841
1295	850	2.564	0.3016	0.099	0.0116	0.0386	1.459	0.1716	0.5690
1297	734	2.252	0.3068	0.132	0.0180	0.0586	1.069	0.1456	0.4747
1309	912	2.458	0.2695	0.085	0.0093	0.0346	1.744	0.1912	0.7095
1311	845	2.191	0.2593	0.087	0.0103	0.0397	1.538	0.1820	0.7020
1315	808	2.429	0.3006	0.083	0.0103	0.0342	1.399	0.1731	0.5760
1319	896	2.317	0.2586	0.066	0.0074	0.0285	1.163	0.1298	0.5019

^e Excluded from the mean

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Terminal

Group, Animal Number	Heart	Heart/BWt	Heart/BrWt	Kidneys	Kidneys/BWt	Kidneys/BrWt	Liver	Liver/BWt	Liver/BrWt
	g	%	ratio	g	%	ratio	g	%	ratio
<u>0 mg/kg/day</u>									
1011	2.256	0.2782	0.9567	5.108	0.6298	2.1662	25.830	3.1850	10.9542
1014	1.928	0.2266	0.8145	6.369	0.7484	2.6907	21.306	2.5036	9.0013
1015	2.119	0.2362	0.9189	5.607	0.6251	2.4315	24.545	2.7363	10.6440
1025	2.375	0.2411	1.0176	7.004	0.7111	3.0009	30.128	3.0587	12.9083
1026	2.042	0.3113	0.9865	6.096	0.9293	2.9449	21.417	3.2648	10.3464
1029	2.390	0.2490	0.8548	7.544	0.7858	2.6981	27.573	2.8722	9.8616
1031	1.872	0.2733	0.7764	4.543	0.6632	1.8843	16.214	2.3670	6.7250
1035	2.181	0.2340	0.9277	5.574	0.5981	2.3709	25.660	2.7532	10.9145
1036	2.139	0.3595	1.0770	5.589	0.9393	2.8142	22.983	3.8627	11.5725
1041	1.951	0.2185	0.7773	5.571	0.6239	2.2195	25.152	2.8166	10.0207
1045	2.435	0.2858	1.0180	5.349	0.6278	2.2362	22.119	2.5961	9.2471
1062	2.342	0.2714	1.0469	6.090	0.7057	2.7224	26.534	3.0746	11.8614
1067	2.091	0.2588	0.8951	6.106	0.7557	2.6139	24.048	2.9762	10.2945
1068	2.138	0.2713	0.9021	6.286	0.7977	2.6523	20.992	2.6640	8.8574
1076	2.538	0.2907	1.1200	6.231	0.7137	2.7498	29.861	3.4205	13.1778
<u>0.1 mg/kg/day</u>									
1091	2.501	0.3357	1.0535	6.730	0.9034	2.8349	35.220	4.7275	14.8357
1093	2.211	0.3466	0.8930	6.921	1.0848	2.7952	25.251	3.9578	10.1983
1094	2.110	0.2387	0.9064	5.023	0.5682	2.1576	22.710	2.5690	9.7552
1096	2.676	0.2561	1.1441	6.986	0.6685	2.9867	26.447	2.5308	11.3070
1097	2.515	0.2577	1.1002	9.562	0.9797	4.1829	34.137	3.4976	14.9331
1099	2.315	0.2695	0.9515	5.983	0.6965	2.4591	25.535	2.9726	10.4953

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Terminal

Group, Animal Number	Heart	Heart/BWt	Heart/BrWt	Kidneys	Kidneys/BWt	Kidneys/BrWt	Liver	Liver/BWt	Liver/BrWt
	g	%	ratio	g	%	ratio	g	%	ratio
<u>0.1 mg/kg/day</u>									
1107	2.416	0.2724	1.0220	6.741	0.7600	2.8515	28.222	3.1817	11.9382
1109	1.869	0.2655	0.8476	4.934	0.7009	2.2376	20.336	2.8886	9.2227
1112	2.400	0.2273	1.0929	6.483	0.6139	2.9522	31.591	2.9916	14.3857
1120	2.466	0.2891	1.0249	6.847	0.8027	2.8458	26.899	3.1535	11.1800
1122	2.469	0.3007	0.9964	6.606	0.8046	2.6659	26.350	3.2095	10.6336
1123	2.591	0.2194	1.0008	6.153	0.5210	2.3766	30.508	2.5832	11.7837
1124	1.960	0.3146	0.8316	4.078	0.6546	1.7302	15.748	2.5278	6.6814
1127	2.455	0.3681	1.1376	27.052 ^e	4.0558 ^e	12.5357 ^e	26.883	4.0304	12.4574
1132	2.116	0.2443	0.9168	6.126	0.7074	2.6542	26.463	3.0558	11.4658
1140	2.428	0.2680	1.1138	5.878	0.6488	2.6963	23.620	2.6071	10.8349
1143	1.876	0.3411	0.8942	7.425	1.3500	3.5391	43.710	7.9473	20.8341
1147	2.146	0.2348	0.8632	5.300	0.5799	2.1319	24.812	2.7147	9.9807
1150	1.876	0.2542	0.8489	5.155	0.6985	2.3326	18.787	2.5457	8.5009
1154	2.145	0.2578	1.1006	5.042	0.6060	2.5870	18.554	2.2300	9.5198
<u>1 mg/kg/day</u>									
1171	1.721	0.2592	0.7358	4.303	0.6480	1.8397	16.959	2.5541	7.2505
1176	1.589	0.2022	0.6891	4.280	0.5445	1.8560	17.372	2.2102	7.5334
1178	2.594	0.3930	1.1722	6.540	0.9909	2.9553	29.686	4.4979	13.4144
1180	2.047	0.2372	0.8966	6.014	0.6969	2.6343	22.514	2.6088	9.8616
1186	2.012	0.3129	0.8464	5.026	0.7816	2.1144	16.463	2.5603	6.9260
1192	2.315	0.2708	1.0176	5.687	0.6651	2.4998	27.361	3.2001	12.0268
1193	2.431	0.3362	1.0323	8.221	1.1371	3.4909	26.110	3.6113	11.0870

^e Excluded from the mean

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Terminal

Group, Animal Number	Heart	Heart/BWt	Heart/BrWt	Kidneys	Kidneys/BWt	Kidneys/BrWt	Liver	Liver/BWt	Liver/BrWt
	g	%	ratio	g	%	ratio	g	%	ratio
<u>1 mg/kg/day</u>									
1194	2.156	0.4759	0.9378	5.432	1.1991	2.3628	18.900	4.1722	8.2210
1199	2.076	0.2779	0.9505	5.413	0.7246	2.4785	21.748	2.9114	9.9579
1204	2.110	0.2730	0.9500	10.193	1.3186	4.5894	36.918	4.7759	16.6222
1211	2.951	0.2990	1.2250	7.373	0.7470	3.0606	33.914	3.4361	14.0780
1212	1.707	0.2544	0.7925	4.391	0.6544	2.0385	20.359	3.0341	9.4517
1218	2.488	0.2837	0.9956	7.799	0.8893	3.1208	25.452	2.9022	10.1849
1221	2.588	0.3570	1.1301	9.500	1.3103	4.1485	28.402	3.9175	12.4026
1223	1.965	0.2178	0.8588	5.311	0.5888	2.3212	22.544	2.4993	9.8531
1225	2.143	0.2235	0.8783	5.447	0.5680	2.2324	24.043	2.5071	9.8537
1227	2.026	0.3093	0.8767	6.436	0.9826	2.7849	21.376	3.2635	9.2497
1240	2.284	0.2891	1.0444	5.585	0.7070	2.5537	23.890	3.0241	10.9236
<u>50 mg/kg/day</u>									
1251	1.821	0.2451	0.7997	4.720	0.6353	2.0729	22.679	3.0524	9.9600
1252	3.466	0.3355	1.4624	7.433	0.7196	3.1363	33.809	3.2729	14.2654
1254	2.303	0.3281	1.0497	3.329	0.4742	1.5173	26.236	3.7373	11.9581
1257	2.192	0.2494	0.9002	6.908	0.7859	2.8370	29.767	3.3865	12.2246
1261	2.184	0.2761	0.8789	5.618	0.7102	2.2608	24.510	3.0986	9.8632
1270	2.460	0.2799	1.0481	6.146	0.6992	2.6187	26.815	3.0506	11.4252
1277	2.338	0.2558	1.0201	6.415	0.7019	2.7989	30.257	3.3104	13.2011
1283	1.980	0.2647	0.8512	5.470	0.7313	2.3517	20.001	2.6739	8.5989
1286	2.218	0.2448	0.9548	7.160	0.7903	3.0822	26.821	2.9604	11.5458
1287	2.252	0.2616	0.9095	6.029	0.7002	2.4350	25.031	2.9072	10.1095

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Terminal

Group, Animal Number	Heart	Heart/BWt	Heart/BrWt	Kidneys	Kidneys/BWt	Kidneys/BrWt	Liver	Liver/BWt	Liver/BrWt
	g	%	ratio	g	%	ratio	g	%	ratio
<u>50 mg/kg/day</u>									
1289	2.316	0.2410	1.0198	5.773	0.6007	2.5421	26.031	2.7087	11.4624
1294	1.925	0.2926	0.9076	4.993	0.7588	2.3541	20.878	3.1729	9.8435
1295	2.384	0.2805	0.9298	9.068	1.0668	3.5367	40.692	4.7873	15.8705
1297	2.538	0.3458	1.1270	6.159	0.8391	2.7349	26.622	3.6270	11.8215
1309	2.317	0.2541	0.9426	6.334	0.6945	2.5769	28.108	3.0820	11.4353
1311	1.740	0.2059	0.7942	6.465	0.7651	2.9507	27.962	3.3091	12.7622
1315	2.152	0.2663	0.8860	5.246	0.6493	2.1597	22.334	2.7641	9.1947
1319	2.081	0.2323	0.8981	6.237	0.6961	2.6918	28.467	3.1771	12.2861

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Terminal

Group, Animal Number	Spleen g	Spleen/BWt %	Spleen/BrWt ratio	Testes g	Testes/BWt %	Testes/BrWt ratio	Thyroid/ parathyroid gl g	Thyroid/ parathyroid gl/ BWt %	Thyroid/ parathyroid gl/ BrWt ratio
<u>0 mg/kg/day</u>									
1011	1.143	0.1409	0.4847	4.016	0.4952	1.7031	0.047	0.0058	0.0200
1014	0.973	0.1143	0.4111	3.070	0.3608	1.2970	0.037	0.0044	0.0157
1015	1.144	0.1275	0.4961	3.873	0.4318	1.6795	0.047	0.0052	0.0203
1025	1.642	0.1667	0.7035	3.446	0.3498	1.4764	0.197	0.0200	0.0846
1026	1.300	0.1982	0.6280	3.848	0.5866	1.8589	0.046	0.0070	0.0223
1029	1.753	0.1826	0.6270	3.669	0.3822	1.3122	0.066	0.0068	0.0235
1031	0.820	0.1197	0.3401	3.260	0.4759	1.3521	0.053	0.0077	0.0218
1035	1.009	0.1083	0.4292	4.104	0.4403	1.7456	0.046	0.0049	0.0194
1036	0.958	0.1610	0.4824	3.430	0.5765	1.7271	0.032	0.0053	0.0159
1041	1.222	0.1368	0.4869	3.389	0.3795	1.3502	0.040	0.0045	0.0159
1045	1.239	0.1454	0.5180	3.905	0.4583	1.6325	0.051	0.0060	0.0215
1062	1.476	0.1710	0.6598	4.111	0.4764	1.8377	0.047	0.0055	0.0211
1067	0.898	0.1111	0.3844	3.495	0.4325	1.4961	0.042	0.0052	0.0180
1068	1.009	0.1280	0.4257	4.037	0.5123	1.7034	0.046	0.0058	0.0194
1076	1.299	0.1488	0.5733	4.337	0.4968	1.9139	0.069	0.0079	0.0303
<u>0.1 mg/kg/day</u>									
1091	1.180	0.1584	0.4971	3.776	0.5068	1.5906	0.072	0.0096	0.0302
1093	1.839	0.2882	0.7427	3.303	0.5177	1.3340	0.171	0.0268	0.0690
1094	1.317	0.1490	0.5657	4.703	0.5320	2.0202	0.038	0.0043	0.0165
1096	1.194	0.1143	0.5105	3.914	0.3745	1.6734	0.127	0.0121	0.0541
1097	1.552	0.1590	0.6789	3.389	0.3472	1.4825	0.243 ^e	0.0249 ^e	0.1064 ^e
1099	1.501	0.1747	0.6169	3.569	0.4155	1.4669	0.050	0.0058	0.0203

^e Excluded from the mean

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Terminal

Group, Animal Number	Spleen g	Spleen/BWt %	Spleen/BrWt ratio	Testes g	Testes/BWt %	Testes/BrWt ratio	Thyroid/ parathyroid gl g	Thyroid/ parathyroid gl/ BWt %	Thyroid/ parathyroid gl/ BrWt ratio
<u>0.1 mg/kg/day</u>									
1107	1.635	0.1843	0.6916	4.042	0.4557	1.7098	0.046	0.0051	0.0192
1109	1.072	0.1523	0.4862	4.027	0.5720	1.8263	0.044	0.0063	0.0201
1112	1.173	0.1111	0.5342	3.537	0.3349	1.6107	0.055	0.0052	0.0249
1120	1.345	0.1577	0.5590	4.219	0.4946	1.7535	0.080	0.0094	0.0332
1122	1.154	0.1406	0.4657	4.706	0.5732	1.8991	0.045	0.0054	0.0180
1123	1.697	0.1437	0.6555	3.502	0.2965	1.3526	0.108	0.0091	0.0417
1124	0.865	0.1388	0.3670	3.322	0.5332	1.4094	0.031	0.0050	0.0133
1127	1.558	0.2336	0.7220	2.799	0.4196	1.2970	0.051	0.0077	0.0238
1132	1.318	0.1522	0.5711	3.873	0.4472	1.6781	0.050	0.0058	0.0216
1140	1.205	0.1330	0.5528	3.976	0.4389	1.8239	0.058	0.0064	0.0265
1143	1.804	0.3280	0.8599	2.964	0.5389	1.4128	0.051	0.0092	0.0241
1147	1.362	0.1490	0.5479	3.590	0.3928	1.4441	0.052	0.0057	0.0208
1150	0.968	0.1312	0.4380	3.375	0.4573	1.5271	0.034	0.0046	0.0152
1154	1.197	0.1439	0.6142	3.056	0.3673	1.5680	0.039	0.0047	0.0200
<u>1 mg/kg/day</u>									
1171	0.882	0.1328	0.3771	1.963	0.2956	0.8392	0.041	0.0062	0.0176
1176	0.996	0.1267	0.4319	3.328	0.4234	1.4432	0.043	0.0055	0.0186
1178	1.075	0.1629	0.4858	3.137	0.4753	1.4175	0.044	0.0067	0.0201
1180	1.171	0.1357	0.5129	3.463	0.4013	1.5169	0.035	0.0041	0.0154
1186	1.185	0.1843	0.4985	3.831	0.5958	1.6117	0.049	0.0075	0.0204
1192	1.366	0.1598	0.6004	3.761	0.4399	1.6532	0.053	0.0062	0.0233
1193	1.341	0.1855	0.5694	3.960	0.5477	1.6815	0.061	0.0084	0.0259

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Terminal

Group, Animal Number	Spleen g	Spleen/BWt %	Spleen/BrWt ratio	Testes g	Testes/BWt %	Testes/BrWt ratio	Thyroid/ parathyroid gl g	Thyroid/ parathyroid gl/ BWt %	Thyroid/ parathyroid gl/ BrWt ratio
<u>1 mg/kg/day</u>									
1194	1.804	0.3982	0.7847	4.324	0.9545	1.8808	0.030	0.0066	0.0130
1199	1.334	0.1786	0.6108	4.274	0.5722	1.9570	0.037	0.0050	0.0171
1204	1.964	0.2541	0.8843	3.676	0.4755	1.6551	0.056	0.0072	0.0252
1211	2.073	0.2100	0.8605	3.344	0.3388	1.3881	0.062	0.0063	0.0258
1212	0.953	0.1420	0.4424	3.494	0.5207	1.6221	0.028	0.0042	0.0130
1218	1.965	0.2241	0.7863	3.350	0.3820	1.3405	0.060	0.0068	0.0240
1221	1.327	0.1830	0.5795	3.787	0.5223	1.6537	0.048	0.0066	0.0209
1223	1.406	0.1559	0.6145	3.966	0.4397	1.7334	0.040	0.0045	0.0176
1225	1.014	0.1057	0.4156	3.962	0.4131	1.6238	0.037	0.0039	0.0153
1227	1.028	0.1569	0.4448	3.507	0.5354	1.5175	0.036	0.0055	0.0155
1240	1.809	0.2290	0.8272	6.309	0.7986	2.8848	0.036	0.0046	0.0165
<u>50 mg/kg/day</u>									
1251	0.781	0.1051	0.3430	3.702	0.4983	1.6258	0.045	0.0061	0.0199
1252	1.403	0.1358	0.5920	3.409	0.3300	1.4384	0.048	0.0046	0.0201
1254	1.586	0.2259	0.7229	3.782	0.5387	1.7238	0.134	0.0191	0.0610
1257	1.222	0.1390	0.5018	3.919	0.4458	1.6094	0.054	0.0061	0.0220
1261	1.150	0.1454	0.4628	4.249	0.5372	1.7099	0.045	0.0056	0.0179
1270	1.192	0.1356	0.5079	4.032	0.4587	1.7179	0.051	0.0058	0.0217
1277	1.312	0.1435	0.5724	6.278	0.6869	2.7391	0.046	0.0050	0.0201
1283	0.922	0.1233	0.3964	4.261	0.5697	1.8319	0.026	0.0035	0.0112
1286	1.333	0.1471	0.5738	3.356	0.3704	1.4447	0.045	0.0050	0.0195
1287	1.043	0.1211	0.4212	3.489	0.4052	1.4091	0.071	0.0083	0.0288

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - MALE

Terminal

Group, Animal Number	Spleen g	Spleen/BWt %	Spleen/BrWt ratio	Testes g	Testes/BWt %	Testes/BrWt ratio	Thyroid/ parathyroid gl g	Thyroid/ parathyroid gl/ BWt %	Thyroid/ parathyroid gl/ BrWt ratio
<u>50 mg/kg/day</u>									
1289	1.200	0.1249	0.5284	3.455	0.3595	1.5214	0.047	0.0049	0.0207
1294	1.148	0.1745	0.5413	3.450	0.5243	1.6266	0.047	0.0071	0.0220
1295	1.281	0.1507	0.4996	2.945	0.3465	1.1486	0.070	0.0082	0.0272
1297	1.225	0.1669	0.5440	5.465	0.7446	2.4267	0.033	0.0044	0.0144
1309	1.165	0.1277	0.4740	4.267	0.4679	1.7360	0.061	0.0067	0.0248
1311	1.445	0.1710	0.6595	3.916	0.4634	1.7873	0.052	0.0062	0.0239
1315	1.136	0.1406	0.4677	4.232	0.5238	1.7423	0.051	0.0063	0.0209
1319	1.475	0.1646	0.6366	5.123	0.5718	2.2110	0.053	0.0059	0.0227

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Terminal

Group, Animal Number	Body weight g	Brain g	Brain/BWt %	Adrenal gl g	Adrenal gl/ BWt %	Adrenal gl/ BrWt ratio	Heart g	Heart/BWt %	Heart/BrWt ratio
<u>0 mg/kg/day</u>									
1333	321	1.864	0.5807	0.065	0.0202	0.0349	1.052	0.3277	0.5644
1335	462	2.078	0.4498	0.111	0.0240	0.0534	1.191	0.2578	0.5731
1339	539	1.939	0.3597	0.099	0.0184	0.0511	1.531	0.2840	0.7896
1347	439	2.015	0.4590	0.114	0.0260	0.0566	1.525	0.3474	0.7568
1352	538	2.192	0.4074	0.160	0.0297	0.0730	1.867	0.3470	0.8517
1353	428	2.027	0.4736	0.097	0.0227	0.0479	1.390	0.3248	0.6857
1355	345	1.942	0.5629	0.076	0.0220	0.0391	1.404	0.4070	0.7230
1357	449	2.093	0.4661	0.087	0.0194	0.0416	1.405	0.3129	0.6713
1358	574	2.164	0.3770	0.110	0.0192	0.0508	1.529	0.2664	0.7066
1365	463	2.007	0.4335	0.101	0.0218	0.0503	1.487	0.3212	0.7409
1368	431	1.872	0.4343	0.135	0.0313	0.0721	1.345	0.3121	0.7185
1370	356	1.986	0.5579	0.068	0.0191	0.0342	1.112	0.3124	0.5599
1372	511	1.841	0.3603	0.105	0.0205	0.0570	1.644	0.3217	0.8930
1374	547	2.051	0.3750	0.147	0.0269	0.0717	1.468	0.2684	0.7157
1389	510	1.904	0.3733	0.068	0.0133	0.0357	1.461	0.2865	0.7673
1392	479	1.910	0.3987	0.054	0.0113	0.0283	1.598	0.3336	0.8366
<u>1 mg/kg/day</u>									
1416	527	2.093	0.3972	0.104	0.0197	0.0497	1.366	0.2592	0.6527
1418	587	2.026	0.3451	0.087	0.0148	0.0429	1.264	0.2153	0.6239
1419	545	2.130	0.3908	0.150	0.0275	0.0704	1.350	0.2477	0.6338
1424	394	2.069	0.5251	0.100	0.0254	0.0483	1.056	0.2680	0.5104
1425	463	2.098	0.4531	0.076	0.0164	0.0362	1.433	0.3095	0.6830

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Terminal

Group, Animal Number	Body weight g	Brain g	Brain/BWt %	Adrenal gl g	Adrenal gl/ BWt %	Adrenal gl/ BrWt ratio	Heart g	Heart/BWt %	Heart/BrWt ratio
<u>1 mg/kg/day</u>									
1429	434	1.906	0.4392	0.114	0.0263	0.0598	1.390	0.3203	0.7293
1430	689	2.041	0.2962	0.152	0.0221	0.0745	1.853	0.2689	0.9079
1431	492	2.178	0.4427	0.159	0.0323	0.0730	1.485	0.3018	0.6818
1432	513	2.003	0.3904	0.105	0.0205	0.0524	1.620	0.3158	0.8088
1434	388	1.940	0.5000	0.075	0.0193	0.0387	1.600	0.4124	0.8247
1435	626	1.850	0.2955	0.053	0.0085	0.0286	1.696	0.2709	0.9168
1437	399	1.939	0.4860	0.178	0.0446	0.0918	1.093	0.2739	0.5637
1438	569	2.060	0.3620	0.062	0.0109	0.0301	1.341	0.2357	0.6510
1440	530	2.053	0.3874	0.056	0.0106	0.0273	1.323	0.2496	0.6444
1447	477	1.965	0.4119	0.115	0.0241	0.0585	1.390	0.2914	0.7074
1450	538	2.143	0.3983	0.083	0.0154	0.0387	1.475	0.2742	0.6883
1454	442	1.920	0.4344	0.059	0.0133	0.0307	1.445	0.3269	0.7526
1460	546	2.059	0.3771	0.157	0.0288	0.0763	1.641	0.3005	0.7970
1467	491	2.092	0.4261	0.069	0.0141	0.0330	1.380	0.2811	0.6597
1469	302	1.869	0.6189	0.109	0.0361	0.0583	1.627	0.5387	0.8705
1471	330	2.009	0.6088	0.095	0.0288	0.0473	1.364	0.4133	0.6789
1475	325	2.205	0.6785	0.058	0.0178	0.0263	1.007	0.3098	0.4567
<u>50 mg/kg/day</u>									
1491	631	2.070	0.3281	0.070	0.0111	0.0338	1.690	0.2678	0.8164
1496	543	2.214	0.4077	0.098	0.0180	0.0443	1.637	0.3015	0.7394
1500	476	1.957	0.4111	0.045	0.0095	0.0230	1.198	0.2517	0.6122
1516	438	1.891	0.4317	0.104	0.0237	0.0550	1.711	0.3906	0.9048

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Terminal

Group, Animal Number	Body weight g	Brain g	Brain/BWt %	Adrenal gl g	Adrenal gl/ BWt %	Adrenal gl/ BrWt ratio	Heart g	Heart/BWt %	Heart/BrWt ratio
<u>50 mg/kg/day</u>									
1520	653	1.868	0.2861	0.068	0.0104	0.0364	1.527	0.2338	0.8175
1528	507	2.085	0.4112	0.137	0.0270	0.0657	2.422	0.4777	1.1616
1532	463	1.911	0.4127	0.114	0.0246	0.0597	1.271	0.2745	0.6651
1538	546	2.116	0.3875	0.512 ^e	0.0938 ^e	0.2420 ^e	2.037	0.3731	0.9627
1541	510	1.910	0.3745	0.282	0.0553	0.1476	1.615	0.3167	0.8455
1543	484	2.026	0.4186	0.113	0.0233	0.0558	1.383	0.2857	0.6826
1546	544	1.994	0.3665	0.119	0.0219	0.0597	1.807	0.3322	0.9062
1547	474	1.904	0.4017	0.123	0.0259	0.0646	1.444	0.3046	0.7584
1549	590	1.750	0.2966	0.115	0.0195	0.0657	1.521	0.2578	0.8691
1553	525	2.141	0.4078	0.166	0.0316	0.0775	1.516	0.2888	0.7081
1559	399	1.935	0.4850	0.070	0.0175	0.0362	1.242	0.3113	0.6419
<u>500 mg/kg/day</u>									
1576	466	1.924	0.4129	0.089	0.0191	0.0463	1.375	0.2951	0.7147
1578	382	1.938	0.5073	0.101	0.0264	0.0521	1.586	0.4152	0.8184
1581	419	2.104	0.5021	0.102	0.0243	0.0485	1.293	0.3086	0.6145
1585	424	2.007	0.4733	0.082	0.0193	0.0409	1.345	0.3172	0.6702
1587	601	2.176	0.3621	0.145	0.0241	0.0666	1.891	0.3146	0.8690
1593	479	2.359	0.4925	0.395	0.0825	0.1674	1.731	0.3614	0.7338
1594	369	1.743	0.4724	0.086	0.0233	0.0493	1.441	0.3905	0.8267
1595	365	1.970	0.5397	0.329	0.0901	0.1670	1.243	0.3405	0.6310
1607	669	1.902	0.2843	0.085	0.0127	0.0447	1.832	0.2738	0.9632
1612	484	9.268	1.9149	0.061	0.0126	0.0066	1.527	0.3155	0.1648

^e Excluded from the mean

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Terminal

Group, Animal Number	Body weight g	Brain g	Brain/BWt %	Adrenal gl g	Adrenal gl/ BWt %	Adrenal gl/ BrWt ratio	Heart g	Heart/BWt %	Heart/BrWt ratio
<u>500 mg/kg/day</u>									
1613	570	1.922	0.3372	0.157	0.0275	0.0817	1.417	0.2486	0.7373
1618	477	1.845	0.3868	0.115	0.0241	0.0623	2.012	0.4218	1.0905
1621	425	2.003	0.4713	0.050	0.0118	0.0250	1.368	0.3219	0.6830
1623	510	2.000	0.3922	0.210	0.0412	0.1050	1.687	0.3308	0.8435
1628	418	2.051	0.4907	0.051	0.0122	0.0249	1.358	0.3249	0.6621
1631	412	1.873	0.4546	0.066	0.0160	0.0352	1.257	0.3051	0.6711
1632	364	2.110	0.5797	0.050	0.0137	0.0237	1.298	0.3566	0.6152
1633	388	2.009	0.5178	0.100	0.0258	0.0498	1.349	0.3477	0.6715

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Terminal

Group, Animal Number	Kidneys	Kidneys/BWt	Kidneys/BrWt	Liver	Liver/BWt	Liver/BrWt	Ovaries w/ oviducts	Ovaries w/ oviducts/BWt	Ovaries w/ oviducts/BrWt
	g	%	ratio	g	%	ratio	g	%	ratio
<u>0 mg/kg/day</u>									
1333	2.436	0.7589	1.3069	9.324	2.9047	5.0021	0.098	0.0305	0.0526
1335	2.807	0.6076	1.3508	17.755	3.8431	8.5443	0.107	0.0232	0.0515
1339	2.912	0.5403	1.5018	16.712	3.1006	8.6189	0.200	0.0371	0.1031
1347	3.466	0.7895	1.7201	14.753	3.3606	7.3216	0.115	0.0262	0.0571
1352	3.907	0.7262	1.7824	22.066	4.1015	10.0666	0.158	0.0294	0.0721
1353	3.229	0.7544	1.5930	15.168	3.5439	7.4830	0.129	0.0301	0.0636
1355	3.134	0.9084	1.6138	9.632	2.7919	4.9598	0.085	0.0246	0.0438
1357	3.144	0.7002	1.5022	14.981	3.3365	7.1577	0.143	0.0318	0.0683
1358	3.336	0.5812	1.5416	19.727	3.4368	9.1160	0.114	0.0199	0.0527
1365	3.422	0.7391	1.7050	17.955	3.8780	8.9462	0.162	0.0350	0.0807
1368	3.157	0.7325	1.6864	17.905	4.1543	9.5646	0.149	0.0346	0.0796
1370	2.673	0.7508	1.3459	11.548	3.2438	5.8147	0.101	0.0284	0.0509
1372	2.830	0.5538	1.5372	21.715	4.2495	11.7952	0.162	0.0317	0.0880
1374	3.152	0.5762	1.5368	19.068	3.4859	9.2969	0.128	0.0234	0.0624
1389	3.127	0.6131	1.6423	18.184	3.5655	9.5504	0.103	0.0202	0.0541
1392	2.923	0.6102	1.5304	15.568	3.2501	8.1508	0.032	0.0067	0.0168
<u>1 mg/kg/day</u>									
1416	3.119	0.5918	1.4902	17.875	3.3918	8.5404	0.196	0.0372	0.0936
1418	2.920	0.4974	1.4413	13.700	2.3339	6.7621	0.145	0.0247	0.0716
1419	3.420	0.6275	1.6056	19.790	3.6312	9.2911	0.120	0.0220	0.0563
1424	2.437	0.6185	1.1779	8.608	2.1848	4.1605	0.079	0.0201	0.0382
1425	3.565	0.7700	1.6992	14.178	3.0622	6.7579	0.133	0.0287	0.0634

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Terminal

Group, Animal Number	Kidneys g	Kidneys/BWt %	Kidneys/BrWt ratio	Liver g	Liver/BWt %	Liver/BrWt ratio	Ovaries w/ oviducts g	Ovaries w/ oviducts/BWt %	Ovaries w/ oviducts/BrWt ratio
<u>1 mg/kg/day</u>									
1429	2.874	0.6622	1.5079	18.428	4.2461	9.6684	0.136	0.0313	0.0714
1430	3.895	0.5653	1.9084	21.474	3.1167	10.5213	0.144	0.0209	0.0706
1431	3.780	0.7683	1.7355	17.446	3.5459	8.0101	0.167	0.0339	0.0767
1432	3.992	0.7782	1.9930	20.912	4.0764	10.4403	0.110	0.0214	0.0549
1434	2.980	0.7680	1.5361	13.176	3.3959	6.7918	0.098	0.0253	0.0505
1435	3.282	0.5243	1.7741	25.254	4.0342	13.6508	0.125	0.0200	0.0676
1437	3.257	0.8163	1.6797	12.858	3.2226	6.6313	0.090	0.0226	0.0464
1438	2.983	0.5243	1.4481	13.424	2.3592	6.5165	0.123	0.0216	0.0597
1440	2.991	0.5643	1.4569	22.315	4.2104	10.8695	0.156	0.0294	0.0760
1447	3.382	0.7090	1.7211	10.424	2.1853	5.3048	0.075	0.0157	0.0382
1450	3.027	0.5626	1.4125	15.419	2.8660	7.1951	0.666	0.1238	0.3108
1454	2.766	0.6258	1.4406	13.901	3.1450	7.2401	0.090	0.0204	0.0469
1460	3.547	0.6496	1.7227	16.535	3.0284	8.0306	0.155	0.0284	0.0753
1467	2.694	0.5487	1.2878	15.420	3.1405	7.3709	0.111	0.0226	0.0531
1469	5.557 ^e	1.8401 ^e	2.9732 ^e	14.288	4.7311	7.6447	0.145	0.0480	0.0776
1471	3.124	0.9467	1.5550	11.837	3.5870	5.8920	0.080	0.0242	0.0398
1475	2.843	0.8748	1.2893	10.380	3.1938	4.7075	0.133	0.0409	0.0603
<u>50 mg/kg/day</u>									
1491	3.350	0.5309	1.6184	20.770	3.2916	10.0338	0.080	0.0127	0.0386
1496	2.916	0.5370	1.3171	20.636	3.8004	9.3207	0.159	0.0293	0.0718
1500	2.709	0.5691	1.3843	12.943	2.7191	6.6137	0.126	0.0265	0.0644
1516	3.267	0.7459	1.7277	15.510	3.5411	8.2020	0.091	0.0208	0.0481

^e Excluded from the mean

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Terminal

Group, Animal Number	Kidneys g	Kidneys/BWt %	Kidneys/BrWt ratio	Liver g	Liver/BWt %	Liver/BrWt ratio	Ovaries w/ oviducts g	Ovaries w/ oviducts/BWt %	Ovaries w/ oviducts/BrWt ratio
<u>50 mg/kg/day</u>									
1520	2.612	0.4000	1.3983	16.307	2.4972	8.7297	0.139	0.0213	0.0744
1528	7.095 ^e	1.3994 ^e	3.4029 ^e	23.354	4.6063	11.2010	0.093	0.0183	0.0446
1532	3.237	0.6991	1.6939	17.668	3.8160	9.2454	0.171	0.0369	0.0895
1538	3.693	0.6764	1.7453	18.982	3.4766	8.9707	0.120	0.0220	0.0567
1541	3.675	0.7206	1.9241	19.133	3.7516	10.0173	0.124	0.0243	0.0649
1543	3.123	0.6452	1.5415	16.478	3.4045	8.1333	0.141	0.0291	0.0696
1546	3.470	0.6379	1.7402	16.448	3.0235	8.2487	0.094	0.0173	0.0471
1547	3.112	0.6565	1.6345	16.501	3.4812	8.6665	0.082	0.0173	0.0431
1549	3.440	0.5831	1.9657	14.877	2.5215	8.5011	0.104	0.0176	0.0594
1553	3.765	0.7171	1.7585	16.996	3.2373	7.9383	0.107	0.0204	0.0500
1559	3.088	0.7739	1.5959	11.618	2.9118	6.0041	0.084	0.0211	0.0434
<u>500 mg/kg/day</u>									
1576	2.993	0.6423	1.5556	26.470	5.6803	13.7578	0.126	0.0270	0.0655
1578	3.761	0.9846	1.9407	18.315	4.7945	9.4505	0.094	0.0246	0.0485
1581	3.213	0.7668	1.5271	17.644	4.2110	8.3859	0.112	0.0267	0.0532
1585	3.273	0.7719	1.6308	21.075	4.9705	10.5007	0.127	0.0300	0.0633
1587	4.128	0.6869	1.8971	44.557	7.4138	20.4766	0.127	0.0211	0.0584
1593	4.687	0.9785	1.9869	27.766	5.7967	11.7702	0.136	0.0284	0.0577
1594	3.321	0.9000	1.9053	15.739	4.2653	9.0298	0.150	0.0407	0.0861
1595	3.009	0.8244	1.5274	14.012	3.8389	7.1127	0.121	0.0332	0.0614
1607	4.803	0.7179	2.5252	34.820	5.2048	18.3070	0.081	0.0121	0.0426
1612	3.312	0.6843	0.3574	26.926	5.5632	2.9053	0.126	0.0260	0.0136

^e Excluded from the mean

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Terminal

Group, Animal Number	Kidneys	Kidneys/BWt	Kidneys/BrWt	Liver	Liver/BWt	Liver/BrWt	Ovaries w/ oviducts	Ovaries w/ oviducts/BWt	Ovaries w/ oviducts/BrWt
	g	%	ratio	g	%	ratio	g	%	ratio
<u>500 mg/kg/day</u>									
1613	3.590	0.6298	1.8678	35.592	6.2442	18.5182	0.165	0.0289	0.0858
1618	3.698	0.7753	2.0043	20.344	4.2650	11.0266	0.153	0.0321	0.0829
1621	3.004	0.7068	1.4998	19.179	4.5127	9.5751	0.166	0.0391	0.0829
1623	4.031	0.7904	2.0155	24.393	4.7829	12.1965	0.444	0.0871	0.2220
1628	3.128	0.7483	1.5251	16.618	3.9756	8.1024	0.261	0.0624	0.1273
1631	3.114	0.7558	1.6626	19.771	4.7988	10.5558	0.198	0.0481	0.1057
1632	2.835	0.7788	1.3436	16.494	4.5313	7.8171	0.156	0.0429	0.0739
1633	3.412	0.8794	1.6984	18.464	4.7588	9.1906	0.110	0.0284	0.0548

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Terminal

Group, Animal Number	Spleen g	Spleen/BWt %	Spleen/BrWt ratio	Thyroid/ parathyroid gl g	Thyroid/ parathyroid gl/ BWt %	Thyroid/ parathyroid gl/ BrWt ratio	Uterus w/ cervix g	Uterus w/ cervix/BWt %	Uterus w/ cervix/BrWt ratio
<u>0 mg/kg/day</u>									
1333	0.390	0.1215	0.2092	0.022	0.0069	0.0118	9.209	2.8688	4.9405
1335	0.955	0.2067	0.4596	0.032	0.0070	0.0155	0.974	0.2108	0.4687
1339	0.931	0.1727	0.4801	0.034	0.0064	0.0177	1.048	0.1944	0.5405
1347	0.854	0.1945	0.4238	0.033	0.0075	0.0163	1.774	0.4041	0.8804
1352	1.454	0.2703	0.6633	0.045	0.0084	0.0207	1.408	0.2617	0.6423
1353	0.584	0.1364	0.2881	0.038	0.0089	0.0188	1.405	0.3283	0.6931
1355	0.480	0.1391	0.2472	0.041	0.0119	0.0212	0.596	0.1728	0.3069
1357	0.791	0.1762	0.3779	0.042	0.0094	0.0203	1.689	0.3762	0.8070
1358	1.145	0.1995	0.5291	0.075	0.0131	0.0348	1.875	0.3267	0.8665
1365	1.461	0.3156	0.7280	0.053	0.0114	0.0264	0.937	0.2024	0.4669
1368	1.010	0.2343	0.5395	0.035	0.0080	0.0184	1.421	0.3297	0.7591
1370	0.744	0.2090	0.3746	0.027	0.0074	0.0133	1.435	0.4031	0.7226
1372	1.420	0.2779	0.7713	0.048	0.0094	0.0261	0.708	0.1386	0.3846
1374	0.697	0.1274	0.3398	0.034	0.0062	0.0165	1.704	0.3115	0.8308
1389	0.989	0.1939	0.5194	0.049	0.0096	0.0258	1.552	0.3043	0.8151
1392	0.668	0.1395	0.3497	0.054	0.0113	0.0284	1.073	0.2240	0.5618
<u>1 mg/kg/day</u>									
1416	0.666	0.1264	0.3182	0.036	0.0069	0.0174	1.818	0.3450	0.8686
1418	0.638	0.1087	0.3149	0.041	0.0070	0.0203	0.632	0.1077	0.3119
1419	0.750	0.1376	0.3521	0.035	0.0065	0.0166	1.260	0.2312	0.5915
1424	0.567	0.1439	0.2740	0.072	0.0183	0.0349	1.067	0.2708	0.5157
1425	0.844	0.1823	0.4023	0.043	0.0092	0.0203	0.929	0.2006	0.4428

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Terminal

Group, Animal Number	Spleen g	Spleen/BWt %	Spleen/BrWt ratio	Thyroid/ parathyroid gl g	Thyroid/ parathyroid gl/ BWt %	Thyroid/ parathyroid gl/ BrWt ratio	Uterus w/ cervix g	Uterus w/ cervix/BWt %	Uterus w/ cervix/BrWt ratio
<u>1 mg/kg/day</u>									
1429	0.681	0.1569	0.3573	0.045	0.0103	0.0236	1.410	0.3249	0.7398
1430	1.286	0.1866	0.6301	0.041	0.0059	0.0199	1.128	0.1637	0.5527
1431	1.014	0.2061	0.4656	0.043	0.0087	0.0196	1.196	0.2431	0.5491
1432	1.770	0.3450	0.8837	0.083	0.0161	0.0413	1.101	0.2146	0.5497
1434	0.555	0.1430	0.2861	0.027	0.0071	0.0141	0.983	0.2534	0.5067
1435	0.991	0.1583	0.5357	0.038	0.0061	0.0205	0.673	0.1075	0.3638
1437	0.499	0.1251	0.2573	0.045	0.0113	0.0233	0.832	0.2085	0.4291
1438	0.850	0.1494	0.4126	0.050	0.0088	0.0244	0.570	0.1002	0.2767
1440	0.881	0.1662	0.4291	0.029	0.0055	0.0142	0.680	0.1283	0.3312
1447	0.555	0.1164	0.2824	0.075	0.0158	0.0383	0.559	0.1172	0.2845
1450	0.780	0.1450	0.3640	0.043	0.0080	0.0201	0.789	0.1467	0.3682
1454	0.976	0.2208	0.5083	0.041	0.0093	0.0214	0.725	0.1640	0.3776
1460	0.530	0.0971	0.2574	0.050	0.0092	0.0244	1.093	0.2002	0.5308
1467	0.788	0.1605	0.3767	0.031	0.0063	0.0148	3.369	0.6862	1.6104
1469	0.610	0.2020	0.3264	0.041	0.0135	0.0218	2.978	0.9861	1.5934
1471	0.910	0.2758	0.4530	0.043	0.0130	0.0213	1.417	0.4294	0.7053
1475	0.711	0.2188	0.3224	0.046	0.0142	0.0209	0.854	0.2628	0.3873
<u>50 mg/kg/day</u>									
1491	0.890	0.1410	0.4300	0.042	0.0067	0.0205	0.450	0.0713	0.2174
1496	1.248	0.2298	0.5637	0.033	0.0060	0.0148	1.471	0.2709	0.6644
1500	0.504	0.1059	0.2575	0.037	0.0077	0.0188	0.894	0.1878	0.4568
1516	0.996	0.2274	0.5267	0.046	0.0104	0.0241	2.421	0.5527	1.2803

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Terminal

Group, Animal Number	Spleen g	Spleen/BWt %	Spleen/BrWt ratio	Thyroid/ parathyroid gl g	Thyroid/ parathyroid gl/ BWt %	Thyroid/ parathyroid gl/ BrWt ratio	Uterus w/ cervix g	Uterus w/ cervix/BWt %	Uterus w/ cervix/BrWt ratio
<u>50 mg/kg/day</u>									
1520	0.765	0.1172	0.4095	0.041	0.0063	0.0220	0.929	0.1423	0.4973
1528	3.547	0.6996	1.7012	0.037	0.0074	0.0179	2.908	0.5736	1.3947
1532	0.713	0.1540	0.3731	0.047	0.0102	0.0247	0.651	0.1406	0.3407
1538	1.186	0.2172	0.5605	0.038	0.0070	0.0181	1.254	0.2297	0.5926
1541	0.942	0.1847	0.4932	0.039	0.0077	0.0205	0.954	0.1871	0.4995
1543	0.781	0.1614	0.3855	0.055	0.0113	0.0269	0.947	0.1957	0.4674
1546	0.723	0.1329	0.3626	0.040	0.0074	0.0201	2.272	0.4176	1.1394
1547	0.670	0.1414	0.3519	0.040	0.0084	0.0209	0.963	0.2032	0.5058
1549	0.743	0.1259	0.4246	0.051	0.0086	0.0291	0.986	0.1671	0.5634
1553	0.863	0.1644	0.4031	0.044	0.0084	0.0206	1.422	0.2709	0.6642
1559	0.772	0.1935	0.3990	0.046	0.0115	0.0237	0.625	0.1566	0.3230
<u>500 mg/kg/day</u>									
1576	0.487	0.1045	0.2531	0.036	0.0077	0.0186	0.774	0.1661	0.4023
1578	0.555	0.1453	0.2864	0.034	0.0089	0.0176	1.795	0.4699	0.9262
1581	0.521	0.1243	0.2476	0.039	0.0092	0.0183	0.634	0.1513	0.3013
1585	0.600	0.1415	0.2990	0.044	0.0104	0.0220	1.022	0.2410	0.5092
1587	0.944	0.1571	0.4338	0.054	0.0090	0.0247	1.303	0.2168	0.5988
1593	0.817	0.1706	0.3463	0.046	0.0096	0.0195	1.667	0.3480	0.7067
1594	0.618	0.1675	0.3546	0.034	0.0092	0.0196	1.591	0.4312	0.9128
1595	0.505	0.1384	0.2563	0.042	0.0115	0.0214	0.571	0.1564	0.2898
1607	0.812	0.1214	0.4269	0.029	0.0043	0.0153	0.900	0.1345	0.4732
1612	7.924 ^e	1.6372 ^e	0.8550 ^e	0.034	0.0071	0.0037	0.668	0.1380	0.0721

^e Excluded from the mean

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Final Body and Organ Weights - FEMALE

Terminal

Group, Animal Number	Spleen g	Spleen/BWt %	Spleen/BrWt ratio	Thyroid/ parathyroid gl g	Thyroid/ parathyroid gl/ BWt %	Thyroid/ parathyroid gl/ BrWt ratio	Uterus w/ cervix g	Uterus w/ cervix/BWt %	Uterus w/ cervix/BrWt ratio
<u>500 mg/kg/day</u>									
1613	1.136	0.1993	0.5911	0.047	0.0082	0.0245	1.173	0.2058	0.6103
1618	0.395	0.0828	0.2141	0.045	0.0094	0.0242	1.389	0.2912	0.7528
1621	0.666	0.1567	0.3325	0.041	0.0096	0.0204	0.698	0.1642	0.3485
1623	0.785	0.1539	0.3925	0.046	0.0090	0.0229	0.865	0.1696	0.4325
1628	0.588	0.1407	0.2867	0.030	0.0071	0.0145	1.650	0.3947	0.8045
1631	0.562	0.1364	0.3001	0.047	0.0115	0.0253	0.845	0.2051	0.4511
1632	0.702	0.1929	0.3327	0.033	0.0091	0.0157	0.915	0.2514	0.4336
1633	0.717	0.1848	0.3569	0.047	0.0121	0.0233	1.458	0.3758	0.7257

Table 10
Individual Animal Listing

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1001	S	Macroscopic all tissues	- within normal limits
1001	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain coagulating glands epididymides esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1001	S	Microscopic joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric nerve, sciatic nose, level a nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - infiltration, mononuclear cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1001	S	Microscopic pituitary gland prostate gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1001	S	Microscopic thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1002	S	Macroscopic all tissues	- within normal limits
1002	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain coagulating glands	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1002	S	Microscopic epididymides esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric	 - within normal limits - within normal limits - within normal limits - within normal limits - degeneration/atrophy, retina, unilateral, minimal - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - infiltration, mononuclear cell, minimal - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1002	S	Microscopic nerve, sciatic nose, level a nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx pituitary gland prostate gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - fibrosis, minimal - within normal limits one of pair present - within normal limits - hyperplasia, focal, pars distalis, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1002	S	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1003	S	Macroscopic all tissues	- within normal limits
1003	S	Microscopic adrenal glands	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1003	S	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain coagulating glands epididymides esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - nephropathy, chronic progressive, bilateral, moderate - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1003	S	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric nerve, sciatic nose, level a nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx pituitary gland prostate gland salivary gland, mandibular	- within normal limits - within normal limits - within normal limits - infiltration, mononuclear cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - fibrosis, minimal - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1003	S	Microscopic salivary gland, parotid salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus thyroid gland tongue trachea	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1003	S	Microscopic ureters urinary bladder	- within normal limits - within normal limits
1004	S	Macroscopic all tissues	- within normal limits
1004	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain coagulating glands epididymides esophagus eyes	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - astrocytoma, malignant, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1004	S	Microscopic eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric nerve, sciatic nose, level a	- within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - infiltration, mononuclear cell, minimal - vacuolation, centrilobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1004	S	Microscopic nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx pituitary gland prostate gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1004	S	Microscopic spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1005	S	Macroscopic spleen	- irregular surface, mild there is a constriction in the center of the spleen.
1005	S	Microscopic adrenal glands	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1005	S	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain coagulating glands epididymides esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - nephropathy, chronic progressive, bilateral, moderate - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1005	S	Microscopic salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus thyroid gland tongue trachea	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits abnormal shape, no lesion. - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1005	S	Microscopic ureters urinary bladder non-correlated macro observation	- within normal limits - within normal limits - spleen - irregular surface
1006	S	Macroscopic all tissues	- within normal limits
1006	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain coagulating glands epididymides esophagus	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1006	S	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric nerve, sciatic	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - nephropathy, chronic progressive, bilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - infiltration, mononuclear cell, minimal - vacuolation, centrilobular, minimal - hyperplasia, type II cell, minimal - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1006	S	Microscopic nose, level a nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx pituitary gland prostate gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	 - within normal limits - within normal limits - within normal limits - within normal limits - fibrosis, minimal - not examined - within normal limits - cyst, mild - hyperplasia, focal, pars distalis, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1006	S	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1007	S	Macroscopic all tissues	- within normal limits
1007	S	Microscopic adrenal glands	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1007	S	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain coagulating glands epididymides esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - inflammation, acute, unilateral, mild - nephropathy, chronic progressive, bilateral, mild - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1007	S	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric nerve, sciatic nose, level a nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx	- within normal limits - within normal limits - within normal limits - within normal limits - infiltration, mononuclear cell, minimal - vacuolation, periportal, minimal - within normal limits - within normal limits - hemangiosarcoma, malignant, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1007	S	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		prostate gland	- within normal limits
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		seminal vesicles	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		testes	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1007	S	Microscopic thymus thyroid gland tongue trachea ureters urinary bladder	- depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1008	S	Macroscopic all tissues	- within normal limits
1008	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1008	S	Microscopic coagulating glands epididymides esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - necrosis, focal, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1008	S	Microscopic lymph node, mesenteric nerve, sciatic nose, level a nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx pituitary gland prostate gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - fibrosis, minimal - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1008	S	Microscopic small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1009	S	Macroscopic skin	- hair sparse, left axillary area, right axillary area, moderate corresponds to antemortem observation (hair sparse)

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1009	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain coagulating glands epididymides esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - nephropathy, chronic progressive, bilateral, mild - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1009	S	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric nerve, sciatic nose, level a nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx pituitary gland	- within normal limits - within normal limits - within normal limits - within normal limits - infiltration, mononuclear cell, minimal - vacuolation, centrilobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - fibrosis, minimal - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1009	S	Microscopic prostate gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - alopecia/hypotrichosis, moderate corresponds to macroscopic observation (skin - hair sparse) - hyperplasia, epidermal, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1009	S	Microscopic testes thymus thyroid gland tongue trachea ureters urinary bladder	- hyperplasia, interstitial cell, unilateral, minimal - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1010	S	Macroscopic pituitary gland	- enlarged, red, moderate
1010	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1010	S	Microscopic brain coagulating glands epididymides esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver	- compression, ventral (pituitary tumor), minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - infiltration, mononuclear cell, minimal - vacuolation, centrilobular, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1010	S	Microscopic lung lymph node, mandibular lymph node, mesenteric nerve, sciatic nose, level a nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx pituitary gland prostate gland salivary gland, mandibular salivary gland, parotid	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - fibrosis, minimal - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1010	S	Microscopic salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus thyroid gland tongue trachea ureters	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1010	S	Microscopic urinary bladder	- within normal limits
<u>0.1 mg/kg/day</u> 1081	S	Macroscopic cavity, abdominal	- mass, yellow, mass a, present approximately 4.5 x 2.5 x 2.0 cm. located in the white adipose tissue near the left kidney.
		lymph node, iliac	- within normal limits draining node for mass a, bilateral.
1081	S	Microscopic liver	- infiltration, mononuclear cell, minimal
		lymph node, iliac	- within normal limits
		mesentery/peritoneum	- necrosis, fat, moderate corresponds to macroscopic observation (cavity, abdominal - mass a)
		testes	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0.1 mg/kg/day</u> 1082	S	Macroscopic eyes	- small, left, moderate corresponds to antemortem observation (microphthalmia)
1082	S	eyes, retina harderian glands Microscopic eyes	- small, left, moderate - enlarged, left, mild - phthisis bulbi, unilateral, severe corresponds to macroscopic observation (eyes - small)
		eyes, retina harderian glands liver	- not examined - within normal limits - focus of cellular alteration, clear, minimal - infiltration, mononuclear cell, minimal
		testes non-correlated macro observation	- within normal limits - eyes, retina - small - harderian glands - enlarged
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0.1 mg/kg/day</u>			
1083	S	Macroscopic skin	- nodule, tan, lip, present corresponds to antemortem observation (nodule) approximately 0.3 cm in diameter.
1083	S	Microscopic liver skin testes	- infiltration, mononuclear cell, minimal - papilloma, squamous cell, benign, primary, mortality-independent corresponds to macroscopic observation (skin - nodule) - within normal limits
1084	S	Macroscopic all tissues	- within normal limits
1084	S	Microscopic liver testes	- infiltration, mononuclear cell, minimal - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0.1 mg/kg/day</u>			
1085	S	Macroscopic all tissues	- within normal limits
1085	S	Microscopic liver	- focus of cellular alteration, clear, minimal - infiltration, mononuclear cell, minimal - necrosis, focal, minimal
		testes	- within normal limits
1086	S	Macroscopic all tissues	- within normal limits
1086	S	Microscopic liver	- focus of cellular alteration, clear, minimal - infiltration, mononuclear cell, minimal
		testes	- within normal limits
1087	S	Macroscopic seminal vesicles	- enlarged, left, mild
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0.1 mg/kg/day</u>			
1087	S	Microscopic liver seminal vesicles	- infiltration, mononuclear cell, minimal - dilatation, unilateral, mild corresponds to macroscopic observation (seminal vesicles - enlarged) - inflammation, unilateral, minimal - within normal limits
1088	S	Macroscopic all tissues	- within normal limits
1088	S	Microscopic liver testes	- focus of cellular alteration, eosinophilic, minimal - within normal limits
1089	S	Macroscopic skin	- hair sparse, shoulder, bilateral, mild corresponds to antemortem observation (hair sparse)
1089	S	Microscopic liver	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0.1 mg/kg/day</u>			
1089	S	Microscopic skin	- alopecia/hypotrichosis, minimal corresponds to macroscopic observation (skin - hair sparse)
		testes	- within normal limits
1090	S	Macroscopic all tissues	- within normal limits
1090	S	Microscopic liver	- infiltration, mononuclear cell, minimal
		testes	- within normal limits
<u>1 mg/kg/day</u>			
1161	S	Macroscopic all tissues	- within normal limits
1161	S	Microscopic liver	- hyperplasia, bile duct, minimal - infiltration, mononuclear cell, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1161	S	Microscopic testes	- within normal limits
1162	S	Macroscopic all tissues	- within normal limits
1162	S	Microscopic liver testes	- infiltration, mononuclear cell, minimal - within normal limits
1163	S	Macroscopic all tissues	- within normal limits
1163	S	Microscopic liver testes	- within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1164	S	Macroscopic all tissues	- within normal limits
1164	S	Microscopic liver testes	- infiltration, mononuclear cell, minimal - within normal limits
1165	S	Macroscopic all tissues	- within normal limits
1165	S	Microscopic liver testes	- infiltration, mononuclear cell, minimal - polyarteritis, minimal - within normal limits
1166	S	Macroscopic all tissues	- within normal limits
1166	S	Microscopic liver	- infiltration, mononuclear cell, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1166	S	Microscopic testes	- within normal limits
1167	S	Macroscopic all tissues	- within normal limits
1167	S	Microscopic liver testes	- within normal limits - within normal limits
1168	S	Macroscopic thyroid gland	- enlarged, left, moderate
1168	S	Microscopic liver testes	- infiltration, mononuclear cell, minimal - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1168	S	Microscopic thyroid gland	- carcinoma, follicular cell, malignant, unilateral, primary, incidental, not cause of death corresponds to macroscopic observation (thyroid gland - enlarged)
1169	S	Macroscopic liver	- focus/foci, red, multiple lobes, mild
1169	S	Microscopic liver	- dilatation, sinusoidal, minimal corresponds to macroscopic observation (liver - focus/foci, red)
		testes	- infiltration, mononuclear cell, minimal - within normal limits
1170	S	Macroscopic all tissues	- within normal limits
1170	S	Microscopic liver	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1170	S	Microscopic testes	- within normal limits
<u>50 mg/kg/day</u> 1241	S	Macroscopic all tissues	- within normal limits
1241	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain coagulating glands epididymides esophagus	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1241	S	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - hydronephrosis, bilateral, mild - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - degeneration, cystic, focal, minimal - vacuolation, centrilobular, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1241	S	Microscopic nerve, sciatic nose, level a nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx pituitary gland prostate gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1241	S	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - dilatation, unilateral, mild - within normal limits
1242	S	Macroscopic all tissues	- within normal limits
1242	S	Microscopic adrenal glands	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1242	S	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain coagulating glands epididymides esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1242	S	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric nerve, sciatic nose, level a nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx pituitary gland prostate gland	 - within normal limits - within normal limits - within normal limits - infiltration, mononuclear cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - atrophy, acinar, minimal - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1242	S	Microscopic salivary gland, mandibular salivary gland, parotid salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus thyroid gland tongue	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1242	S	Microscopic trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits
1243	S	Macroscopic all tissues	- within normal limits
1243	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain coagulating glands epididymides esophagus	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1243	S	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric nerve, sciatic	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - infiltration, mononuclear cell, minimal - vacuolation, centrilobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1243	S	Microscopic nose, level a nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx pituitary gland prostate gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1243	S	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1244	S	Macroscopic all tissues	- within normal limits
1244	S	Microscopic adrenal glands	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1244	S	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain coagulating glands epididymides esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1244	S	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric nerve, sciatic nose, level a nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx pituitary gland prostate gland salivary gland, mandibular salivary gland, parotid	 - within normal limits - within normal limits - within normal limits - infiltration, mononuclear cell, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - fibrosis, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1244	S	Microscopic salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus thyroid gland tongue trachea ureters	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1244	S	Microscopic urinary bladder	- within normal limits
1245	S	Macroscopic testes	- focus/foci, yellow, left, mild at junction with head of epididymis.
1245	S	Microscopic adrenal glands	- hyperplasia, focal cortical, unilateral, mild - vacuolation, diffuse, bilateral, minimal - vacuolation, focal, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		coagulating glands	- within normal limits
		epididymides	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1245	S	Microscopic esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, mild - within normal limits - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - infiltration, mononuclear cell, minimal - necrosis, focal, minimal - vacuolation, focal, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1245	S	Microscopic lymph node, mesenteric nerve, sciatic nose, level a nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx pituitary gland prostate gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - atrophy, acinar, minimal - within normal limits - within normal limits - hyperplasia, focal, pars distalis, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - granuloma, foreign body, mild plant material. - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1245	S	Microscopic small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - degeneration/atrophy, seminiferous tubules, unilateral, mild - mineralization, tubular, unilateral, mild corresponds to macroscopic observation (testes - focus/foci, yellow) - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1246	S	Macroscopic stomach, glandular testes	- swollen/thickened, mucosa, mild - enlarged, right, mild
1246	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain coagulating glands epididymides esophagus eyes eyes, optic nerves eyes, retina galt harderian glands	- hyperplasia, focal medullary, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - oligospermia/germ cell debris, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1246	S	Microscopic heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric nerve, sciatic nose, level a nose, level b nose, level c nose, level d pancreas	- within normal limits - within normal limits - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - degeneration, cystic, focal, minimal - necrosis, focal, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1246	S	Microscopic parathyroid glands pharynx pituitary gland prostate gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular	- not examined - within normal limits - hyperplasia, focal, pars distalis, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1246	S	Microscopic testes	- adenoma, interstitial cell, benign, unilateral, primary, incidental, not cause of death corresponds to macroscopic observation (testes - enlarged)
		thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		non-correlated macro observation	- stomach, glandular - swollen/thickened
1247	S	Macroscopic all tissues	- within normal limits
1247	S	Microscopic adrenal glands	- within normal limits
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
S - Scheduled necropsy			

Interim

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1247	S	Microscopic large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric nerve, sciatic nose, level a nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx pituitary gland prostate gland salivary gland, mandibular salivary gland, parotid	- within normal limits - within normal limits - necrosis, focal, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - hyperplasia, focal, pars distalis, mild - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1247	S	Microscopic salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus thyroid gland tongue trachea ureters	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, interstitial cell, unilateral, minimal - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1247	S	Microscopic urinary bladder	- within normal limits
1248	S	Macroscopic liver	- focus/foci, tan, multiple lobes, mild
1248	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain coagulating glands epididymides esophagus eyes eyes, optic nerves	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1248	S	Microscopic eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric nerve, sciatic nose, level a	- within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - necrosis, focal, mild corresponds to macroscopic observation (liver - focus/foci, tan) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1248	S	Microscopic nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx pituitary gland prostate gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar	 - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - hyperplasia, focal, pars distalis, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1248	S	Microscopic spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits
1249 ^r	S	Macroscopic all tissues	- within normal limits
1249 ^r	S	Microscopic adrenal glands	- within normal limits

S - Scheduled necropsy
^r Replacement animal

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1249 ^r	S	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain coagulating glands epididymides esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, mild - nephropathy, chronic progressive, bilateral, mild - within normal limits

S - Scheduled necropsy
^r Replacement animal

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1249 ^r	S	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric nerve, sciatic nose, level a nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx pituitary gland prostate gland	 - within normal limits - within normal limits - within normal limits - within normal limits - degeneration, cystic, focal, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits

S - Scheduled necropsy
^r Replacement animal

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1249 ^r	S	Microscopic salivary gland, mandibular salivary gland, parotid salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus thyroid gland tongue	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, interstitial cell, bilateral, minimal - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits

S - Scheduled necropsy
^r Replacement animal

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1249 ^r	S	Microscopic trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits
1250	S	Macroscopic all tissues	- within normal limits
1250	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain coagulating glands epididymides esophagus	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

S - Scheduled necropsy
^r Replacement animal

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1250	S	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric nerve, sciatic	 - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, focal, unilateral, minimal - cardiomyopathy, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, clear, minimal - necrosis, focal, minimal - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1250	S	Microscopic nose, level a nose, level b nose, level c nose, level d pancreas parathyroid glands pharynx pituitary gland prostate gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual seminal vesicles skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - MALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1250	S	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular testes thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, interstitial cell, unilateral, minimal - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1322	S	Macroscopic all tissues	- within normal limits
1322	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1322	S	Microscopic kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d	- mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, eosinophilic, minimal - hyperplasia, bile duct, mild - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1322	S	Microscopic ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular	 - within normal limits - within normal limits - within normal limits - not examined - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1322	S	Microscopic stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - metaplasia, squamous, minimal - within normal limits
1324	S	Macroscopic all tissues	- within normal limits
1324	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum	- within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1324	S	Microscopic bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1324	S	Microscopic liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid	- focus of cellular alteration, basophilic, minimal - hyperplasia, bile duct, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1324	S	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1324	S	Microscopic vagina	- within normal limits
1325	S	Macroscopic all tissues	- within normal limits
1325	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1325	S	Microscopic harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c	- within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - infiltration, mononuclear cell, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1325	S	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1325	S	Microscopic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1326	S	Macroscopic all tissues	- within normal limits
1326	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1326	S	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, unilateral, minimal - mineralization, tubular, unilateral, minimal - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1326	S	Microscopic large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1326	S	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1326	S	Microscopic uterus with cervix vagina	- within normal limits - within normal limits
1327	S	Macroscopic pituitary gland	- enlarged, mild
1327	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1327	S	Microscopic eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1327	S	Microscopic nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1327	S	Microscopic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation	- within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary gland - enlarged
1328	S	Macroscopic pituitary gland	- enlarged, mild
1328	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1328	S	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum	 - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1328	S	Microscopic	
		larynx	- within normal limits
		liver	- within normal limits
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
			one of pair present
		pharynx	- within normal limits
		pituitary gland	- hyperplasia, diffuse, pars distalis, mild corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1328	S	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1328	S	Microscopic uterus with cervix vagina	- within normal limits - within normal limits
1329	S	Macroscopic all tissues	- within normal limits
1329	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1329	S	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b	- within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1329	S	Microscopic nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1329	S	Microscopic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - metaplasia, squamous, minimal - within normal limits
1330	S	Macroscopic skin	- hair sparse, dorsal cervical region, dorsal thoracic region, moderate corresponds to antemortem observation (hair sparse)
1330	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild
S - Scheduled necropsy			

Interim

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1330	S	Microscopic larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular	 - within normal limits - infiltration, mononuclear cell, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1330	S	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea	- within normal limits - within normal limits - within normal limits - alopecia/hypotrichosis, moderate corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1330	S	Microscopic ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - metaplasia, squamous, minimal - within normal limits
1331	S	Macroscopic all tissues	- within normal limits
1331	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1331	S	Microscopic eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, clear, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1331	S	Microscopic nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1331	S	Microscopic spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1332	S	Macroscopic all tissues	- within normal limits
1332	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal
S - Scheduled necropsy			

Interim

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1332	S	Microscopic larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - vacuolation, median cleft, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - adenocarcinoma, malignant, primary, incidental, not cause of death slide 18. - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u> 1332	S	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- within normal limits
		tongue	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>0 mg/kg/day</u>			
1332	S	Microscopic trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
<u>1 mg/kg/day</u>			
1401	S	Macroscopic all tissues	- within normal limits
1401	S	Microscopic kidneys liver	- within normal limits - within normal limits
1402	S	Macroscopic pituitary gland	- enlarged, red, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1402	S	Macroscopic skin	- hair sparse, dorsal lumbar region, abdominal, mild corresponds to antemortem observation (hair sparse)
1402	S	Microscopic kidneys liver pituitary gland skin non-correlated macro observation	- mineralization, pelvic, bilateral, minimal - hyperplasia, bile duct, minimal - infiltration, mononuclear cell, minimal - within normal limits - alopecia/hypotrichosis, moderate corresponds to macroscopic observation (skin - hair sparse) - pituitary gland - enlarged
1403	S	Macroscopic mammary gland pituitary gland skin	- swollen/thickened, generalized, mild - enlarged, minimal - hair sparse, ventral thorax, dorsal cervical region, mild corresponds to antemortem observation (hair sparse)
1403	S	Microscopic kidneys	- mineralization, pelvic, unilateral, minimal - mineralization, tubular, unilateral, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1403	S	Microscopic liver mammary gland pituitary gland skin non-correlated macro observation	- within normal limits - hyperplasia, lobular, mild corresponds to macroscopic observation (mammary gland - swollen/thickened) - hyperplasia, focal, pars distalis, mild - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - pituitary gland - enlarged
1404	S	Macroscopic all tissues	- within normal limits
1404	S	Microscopic kidneys liver	- within normal limits - focus of cellular alteration, basophilic, minimal
1405	S	Macroscopic lung with bronchi	- focus/foci, white, multiple lobes, mild
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1405	S	Macroscopic lymph node, axillary	- within normal limits draining node for mass a, left.
		lymph node, inguinal	- enlarged, right, moderate
		pituitary gland	- enlarged, mild
		skin, subcutis	- mass, ulcerated, mass a, left axillary area, present corresponds to antemortem observation (mass 1) approximately 2.0 cm in diameter, tan.
1405	S	Microscopic kidneys	- mineralization, pelvic, bilateral, minimal
		liver	- focus of cellular alteration, basophilic, minimal
			- hyperplasia, bile duct, minimal
			- infiltration, mononuclear cell, minimal
		lung	- histiocytosis, alveolar, minimal corresponds to macroscopic observation (lung with bronchi - focus/foci, white)
		lymph node, axillary	- within normal limits
		lymph node, inguinal	- not examined misidentified tissue
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1405	S	Microscopic mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (lymph node, inguinal - enlarged; skin, subcutis - mass a)
		pituitary gland	- hyperplasia, diffuse, pars distalis, mild corresponds to macroscopic observation (pituitary gland - enlarged)
1406	S	Macroscopic all tissues	- within normal limits
1406	S	Microscopic kidneys liver	- mineralization, tubular, unilateral, minimal - infiltration, mononuclear cell, minimal
1407	S	Macroscopic pituitary gland	- enlarged, red, moderate
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1407	S	Microscopic kidneys liver pituitary gland	- mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - infiltration, mononuclear cell, minimal - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
1408	S	Macroscopic all tissues	- within normal limits
1408	S	Microscopic kidneys liver	- nephropathy, chronic progressive, unilateral, minimal - pyelitis, unilateral, minimal - within normal limits
1409	S	Macroscopic pituitary gland	- enlarged, moderate
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1409	S	Microscopic kidneys	- mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, unilateral, minimal
		liver	- infiltration, mononuclear cell, minimal
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
1410	S	Macroscopic pituitary gland	- enlarged, mild
1410	S	Microscopic kidneys	- mineralization, pelvic, unilateral, minimal - nephropathy, chronic progressive, bilateral, mild
		liver	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1481	S	Macroscopic adipose tissue	- focus/foci, yellow, mild located in white adipose tissue near right uterine horn.
		pituitary gland	- enlarged, red, mild
		spleen	- small, mild
1481	S	Microscopic kidneys	- nephropathy, chronic progressive, bilateral, mild
		liver	- within normal limits
		mesentery/peritoneum	- necrosis, fat, mild corresponds to macroscopic observation (adipose tissue - focus/foci, yellow)
		pituitary gland	- within normal limits
		spleen	- within normal limits
		non-correlated macro observation	- pituitary gland - enlarged - spleen - small
1482	S	Macroscopic pituitary gland	- enlarged, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1482	S	Microscopic kidneys	- mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal
		liver	- degeneration, cystic, focal, minimal
		pituitary gland	- within normal limits
		non-correlated macro observation	- pituitary gland - enlarged
1483	S	Macroscopic all tissues	- within normal limits
1483	S	Microscopic kidneys	- mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal
		liver	- focus of cellular alteration, basophilic, minimal - infiltration, mononuclear cell, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1484	S	Macroscopic all tissues	- within normal limits
1484	S	Microscopic kidneys	- mineralization, pelvic, unilateral, minimal - nephropathy, chronic progressive, bilateral, mild - focus of cellular alteration, eosinophilic, mild
		liver	
1485	S	Macroscopic all tissues	- within normal limits
1485	S	Microscopic kidneys	- mineralization, pelvic, bilateral, minimal - infiltration, mononuclear cell, minimal
		liver	
1486	S	Macroscopic all tissues	- within normal limits
1486	S	Microscopic kidneys	- mineralization, pelvic, unilateral, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1486	S	Microscopic liver	- within normal limits
1487	S	Macroscopic skin	- hair sparse, dorsal thoracic region, minimal corresponds to antemortem observation (hair sparse)
1487	S	Microscopic kidneys liver skin	- mineralization, pelvic, bilateral, minimal - within normal limits - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse)
1488	S	Macroscopic lymph node, axillary lymph node, inguinal	- within normal limits draining node for mass b, left. - within normal limits draining node for mass a, right.
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1488	S	Macroscopic ovaries pituitary gland skin skin, subcutis	<ul style="list-style-type: none"> - cyst, clear, left, mild - enlarged, red, severe - abrasion/scab, right inguinal area, mild corresponds to antemortem observation (scabbed area) - hair sparse, neck, shoulder, mild corresponds to antemortem observation (hair sparse) - mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 1.0 x 0.5 x 0.5 cm. - mass, tan, mass b, left axillary area, present corresponds to antemortem observation (swelling) approximately 1.0 cm in diameter.
1488	S	Microscopic kidneys liver lymph node, axillary lymph node, inguinal	<ul style="list-style-type: none"> - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - focus of cellular alteration, eosinophilic, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1488	S	Microscopic mammary gland	- adenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - within normal limits
		ovaries	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		pituitary gland	corresponds to macroscopic observation (pituitary gland - enlarged)
		skin	- alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse)
		non-correlated macro observation	- ovaries - cyst - skin - abrasion/scab
1489	S	Macroscopic liver pituitary gland	- focus/foci, red, multiple lobes, mild - enlarged, red, mild
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1489	S	Macroscopic thyroid gland	- absent, left, no grade
1489	S	Microscopic kidneys liver pituitary gland non-correlated macro observation	- mineralization, pelvic, unilateral, minimal - dilatation, sinusoidal, minimal corresponds to macroscopic observation (liver - focus/foci, red) - hyperplasia, bile duct, minimal - within normal limits - pituitary gland - enlarged
1490	S	Macroscopic lymph node, axillary skin, subcutis	- not identified, right, no grade draining node for mass a. - mass, tan, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 3.0 x 3.0 x 2.0 cm.
1490	S	Microscopic kidneys	- nephropathy, chronic progressive, unilateral, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1490	S	Microscopic liver mammary gland	- within normal limits - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
<u>500 mg/kg/day</u> 1561	S	Macroscopic kidneys pituitary gland	- irregular surface, bilateral, minimal - enlarged, red, mild
1561	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1561	S	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1561	S	Microscopic liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid	- hypertrophy, hepatocyte, centrilobular, mild - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1561	S	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1561	S	Microscopic vagina non-correlated macro observation	- within normal limits - pituitary gland - enlarged
1562	S	Macroscopic pituitary gland	- enlarged, red, severe
1562	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1562	S	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a	- within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1562	S	Microscopic nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1562	S	Microscopic small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1563	S	Macroscopic all tissues	- within normal limits
1563	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1563	S	Microscopic kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries	- mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1563	S	Microscopic oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular	 - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1563	S	Microscopic stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1564	S	Macroscopic all tissues	- within normal limits
1564	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum	- within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1564	S	Microscopic bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, mild
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1564	S	Microscopic lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual	- histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1564	S	Microscopic skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cyst, mild - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1565	S	Macroscopic skin	- hair sparse, left hindleg/limb, left foreleg/limb, mild corresponds to antemortem observation (hair sparse)
1565	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1565	S	Microscopic kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries	- mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1565	S	Microscopic oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen	- within normal limits - within normal limits - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1565	S	Microscopic stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1568	S	Macroscopic lymph node, inguinal skin skin, subcutis	- within normal limits draining node for mass a, right. - hair sparse, left foreleg/limb, right foreleg/limb, mild corresponds to antemortem observation (hair sparse) - mass, tan, mass a, right anogenital region, present corresponds to antemortem observation (mass 1) approximately 2.5 cm in diameter.
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1568	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	- hyperplasia, focal cortical, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1568	S	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries	- within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, mild - histiocytosis, alveolar, minimal - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1568	S	Microscopic oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1568	S	Microscopic stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1569	S	Macroscopic lymph node, inguinal skin, subcutis	- within normal limits draining node for mass a, right. - mass, tan, mass a, right anogenital region, present corresponds to antemortem observation (mass 1) approximately 4.5 x 6.5 x 2.5 cm.
1569	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1569	S	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas	- within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1569	S	Microscopic parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland	- not examined - within normal limits - hyperplasia, focal, pars distalis, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1569	S	Microscopic tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1570	S	Macroscopic all tissues	- within normal limits
1570	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1570	S	Microscopic esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, mild - infiltration, mononuclear cell, minimal - histiocytosis, alveolar, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1570	S	Microscopic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin	 - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1570	S	Microscopic small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cyst, keratin, mild - depletion, lymphoid, generalized, moderate - hyperplasia, c-cell, focal, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1571	S	Macroscopic all tissues	- within normal limits
1571	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1571	S	Microscopic kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries	- mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1571	S	Microscopic oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular	 - within normal limits - within normal limits - not examined - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1571	S	Microscopic thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1572	S	Macroscopic uterus with cervix	- enlarged, body, horn, mild
1572	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1572	S	Microscopic bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1572	S	Microscopic liver	- hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, mild - infiltration, mononuclear cell, minimal - necrosis, focal, minimal
		lung	- histiocytosis, alveolar, minimal
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	one of pair present - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1572	S	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- within normal limits
		tongue	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Interim

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1572	S	Microscopic trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild - hyperplasia, cervical fibromuscular, moderate corresponds to macroscopic observation (uterus with cervix - enlarged) - within normal limits
S - Scheduled necropsy			